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COVER STORY: FATTY LIVER IN NORTHEASTERN CHINA

Letters from the Editors

The year 2016 has without a doubt been a turbulent year in the world, politically, socially, and economically, with lasting reverberations for the state of global health. A devastating Zika epidemic spread in the Americas, just as the world had begun to rebuild from the Ebola outbreak in West Africa. The global refugee crisis intensified, with the Syrian Civil War raging into its sixth year, and Da'esh consolidating power in the Middle East. Meanwhile, voters in the US and UK ushered nationalist movements back into mainstream politics.

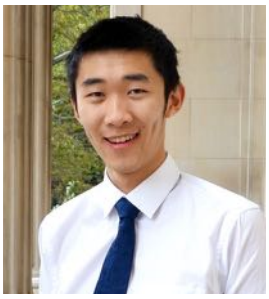
It is easy to become consumed by pessimism, but we must remember the profound link between science and hope: new innovations in smartphone technology may eliminate resource barriers in medical testing. Meanwhile, sustainable and culturally sensitive approaches are being developed to address global health issues, such as fatty liver disease. As of 2016, the number of people living in absolute poverty has halved since the 1980s, and continues to fall, while literacy, nutrition, medicine, and education are making gains. Even when the problems facing the world seem dire, it is incredibly inspiring to watch immensely talented physicians, scientists, policymakers, and others step up to fill the need.

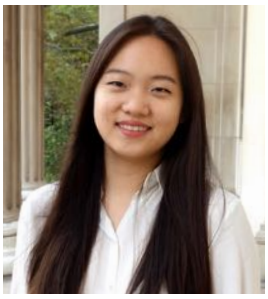
Global health is an inherently and unavoidably politicized field, but we as a journal do not take political positions. Nevertheless, we also firmly believe that questions of fundamental human rights must not become partisan, and we condemn racism, sexism, and xenophobia in all their manifestations. In the coming years, the preservation of independent dialogue about global policies and needs will become more important than ever. No matter the political circumstances, The Journal of Global Health is firmly committed to publishing original global health research, as well as to advocating for human rights, including for immigrants and refugees.

This issue marks The Journal of Global Health's sixth year of leading impactful global health discussions around the world. We are proud to present the product of months of hard work by our authors and JGH. There remains much more research to be done and many more stories to be told. The JGH team continues our mission to promote global health dialogue and impactful research in the form of our physical journal, global health podcasts, and regularly updated content on our website, www.ghjournal.org.

Zhenrui Liao
Diana Ruan

Editors-in-Chief





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Contents

Academic Research Papers

Perspectives

Availability of Resources, Knowledge, Applicability and Preferred Teaching Methods regarding Electrocardiography in a Resource-Limited Clinic in Rural Thailand

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Introduction: Electrocardiography (ECG) is a rapid, non-invasive and inexpensive test requiring minimal training to perform. ECG is used ubiquitously in the developed world to assess the cardiac and metabolic status of Emergency Department (ED) patients; however, its utility in resource-limited settings has not yet been assessed. In order to shed light on ECG utility in developing areas around the world, as well as the perceptions of resources availability, knowledge, applicability and preferred teaching methods regarding ECGs were examined in a resource-limited clinic in Mae Sot, Thailand.

Methods: Focus group discussions and self-administered surveys were conducted among healthcare workers in a clinic in rural Thailand in November 2013.

Results: Five administrative staff and supervising providers participated in focus groups; twenty-nine medics and two physicians participated in the survey. Providers described limited knowledge of ECG interpretation and limited availability of treatments for diagnosed conditions. Providers reported that ECGs are useful when counseling patients and families on prognosis and when deciding when and where to transfer patients to facilities with more resources. Reported preferred training methods include hands-on training, lectures with handouts and specific ECG case examples.

Conclusion: Despite limited treatment options in low-resource settings, ECG can be an informative diagnostic and prognostic tool. Implementation of an ECG educational program at this clinic should focus on training in three areas: ECG interpretation, delivering available treatments even when the "gold standard" treatment is not available, and counseling of patients and family members.

Background

According to the Centers for Disease Control and Prevention, the second most common cause of death in Thailand is coronary artery disease (CAD), plaques form along the walls of the blood vessels that supply heart muscle. CAD accounts for more than 15% of deaths. While the gold standard of care (catheterization for acute ST elevation MI or pacemaker placement for complete heart block) may not be available in resource-poor settings, Electrocardiograms (ECGs) may still assist in making correct diagnoses. Despite these facts, ECG has not been studied in such environments within Thailand. In this study, the authors aim to address the large knowledge gap regarding the diagnostic utility of ECG in this setting, where resources are low but the prevalence of CHD is high.

ECG is a non-invasive bedside test used ubiquitously in cardiac and metabolic assessments of Emergency Department (ED) patients in the developed world. The American Heart Association (AHA) provides guidelines for education and competency in electrocardiography within the United States; however, guidelines for ECG education and competency in resource-limited settings—places that do not have the capability to perform cardiac catheterization or to give thrombolytic agents to open occluded coronary vessels in myocardial infarction—have not yet been published.[1] Yet it has been shown that ECG is a useful modality in these settings as it is quick, noninvasive, inexpensive, and requires minimal training to perform.[2,3]

There are many obstacles to the deployment of ECG for patient assessment in these settings. Some of the limiting factors include the need for trained individuals to accurately read ECG findings and the ongoing need for supplies and maintenance. Some rural and low-resource settings have shown telemedicine—the remote diagnosis and treatment of patients by means of telecommunications technology—to be useful in addressing these issues.[4-6] Such methodology may eliminate some of the resource needs (e.g. paper) and education needs (i.e. ECG interpretation), but still requires an electrocardiography machine and training to operate and maintain it.

Recent exploratory studies have recommended more innovation, education and research on the utility of ECG in the developing world as a potential solution to this lack of resources.[3] ECG can identify patients who would benefit from inexpensive intervention like beta-blockers, ACE inhibitors, and dietary modification.[2,7,8] In addition to identifying coronary artery disease, electrocardiography can also be used to diagnose left ventricular hypertrophy when echocardiography is not readily available,[9] to identify patients with conditions such as Brugada and Long QT Syndromes that put them at risk for sudden

cardiac death and who would benefit from implantable cardioverter defibrillator (ICD) placement and to diagnose of AV block in patients who may require a pacemaker.[10-12]

In addition to being a leading cause of death in Thailand, ischemic heart disease is also the third leading cause of death in Myanmar.[13] As economies and health care systems improve, countries' disease burdens change from infectious disease, sanitation and nutrition to heart disease, stroke, cancer and trauma. Due to this epidemiologic transition, non-communicable diseases are becoming more prevalent in low- and middle-income populations as well.

In Myanmar, total health expenditure is very low at 2.2% of GDP, of which 89.4% is private expenditure; as a result, there are only a small number of healthcare facilities, which are only financially accessible to wealthier populations.[14] For this reason and many others, Burmese people often seek care across the border in Thailand,where free public healthcare is availablean inexpensive lyfunded.[15,16] The study site is a low-resource health clinic that provides medical and social services to a population of approximately 150,000 Burmese refugees and displaced people near the Thai-Burma border at no cost to the patients and their families. There has been no formal assessment of the utility of ECG at this site, despite the availability of ECG machines.

This study's objective was to assess the utility of ECG in one clinic located in a resource-limited setting in Thailand on the border of Myanmar by examining the perceptions of resource availability, knowledge and applicability of ECG and preferred teaching and evaluation methods among staff. A needs assessment on this topic is novel in global health education research and could inform Emergency Medicine (EM) providers interested in working in this area of Thailand and perhaps other resource-limited settings.

Table 1: Example probe questions from focus groups

Do you have medications to treat cardiac rhythm abnormalities?
Do you have medications to treat electrolyte abnormalities?
Do you have transfer capabilities where patients can receive a higher level of care if needed?
Is there a cardiac catheterization lab where patients can be transferred for treatment?
What is the current level of staff training in ECG interpretation?
How do you think training could be improved?
How will you use electrocardiography training to care for patients?

Methods

Study Design

This was an exploratory, descriptive needs-assessment designed to understand the utility of ECG machines in a small clinic located in a resource-limited setting in Thailand. We did not aim to generalize to other sites. We made no hypotheses. As such, no primary or secondary outcome measures were indicated. The Institutional Review Board at Boston University approved this study.

Selection of Participants and Study Setting

Participants in the study included both administrative staff as well as clinical staff among the different subsections of the clinic (including adult, pediatric, obstetric, surgical). Voluntary informed consent was obtained. Only English-speaking subjects were included. This represented about 75% or more of the candidates, as English is often used as a common language given the many dialects of Burmese languages and the unfamiliarity of many with Thai. Participants who could not be present during the study period were excluded. Given the small size of the clinic, the total sample size was limited as there were only about 40 clinical staff, the vast majority included as mentioned above.

The study setting was chosen based on its resource limitations in a population with a presumed high risk of cardiac disease, based upon population statistics from the World Health Organization (WHO) and Centers for Disease Control (CDC).[13,16] The study site is both a clinical and an educational training site open to foreign educators. The clinic serves a target population of about 150,000 people, half of whom are Burmese migrant workers living in Thailand and the other half of whom travel from Myanmar. The clinic provides basic adult, pediatric and obstetric medical and surgical care as well as social services.

Examination Methods

All data was collected at the study setting. Informed consent was obtained from staff willing to participate in focus groups and surveys. No personal identifying data was recorded.

Two separate focus groups were conducted with staff members during a one-month period (November 2013) to ascertain the staff's perceptions of the usefulness of the ECG machine and to determine whether or not they had the ability to treat specific medical problems identified by ECG in patients who present to the clinic. The focus groups were chosen based upon availability of subjects during set times. Efforts were made to include the most senior staff members to obtain the most expansive knowledge of resources, as well as less senior staff to gain a representative sample of all staff; there was no random assignment. The survey asked questions regarding the availability of medications and other diagnostic and treatment resources and perceived comfort level and knowledge of ECG interpretation and treatment of ECG-diagnosed conditions. Examples of these probe questions can be found in Table 1.

Data Analysis

Responses from focus group discussions were recorded and summarized. Survey responses were combined and reported in aggregate. Descriptive statistics were analyzed and reported for survey responses.

Results

Characteristics of Study Subjects

Five administrative staff and supervising health care providers participated in two focus group discussions. The administrative staff physicians participated in one focus group, and three supervising providers participated in another. A total of 35 surveys were distributed and 31 were returned; respondents included 29 medics and two physicians with a mix of both clinical and administrative duties. Many clinic staff members spoke both English and their own native language: Karen, Burmese or another Myanmar state dialect. Participants in the focus groups were separate from the survey respondents.

Survey and Focus Group Results

During the focus group discussions, providers described the potential treatment options for ECG diagnoses including: atrial fibrillation (aspirin, atenolol); heart block (never transfer for pacemaker due to cost); acute coronary syndrome (aspirin, isosorbide dinitrate, atenolol); hyperkalemia (furosemide; never transfer for dialysis due to cost); and hypokalemia (banana). Based upon discussion with the providers, these are treatments that are regularly given for the above diagnoses. Providers felt ECG is useful when determining diagnosis (40% of respondents would use ECG for this purpose), for counseling patients and families on prognosis (50% of respondents would use ECG for this purpose) and when arranging transfer to another facility (40% of respondents would use ECG for this purpose). The most desired training methods, reported similarly in both the survey and focus group, include specific ECG case study examples (86%), lectures with handouts (50%) and hands-on

Fig 1. Surveyed provider-reported availability of medications *available* at the clinic

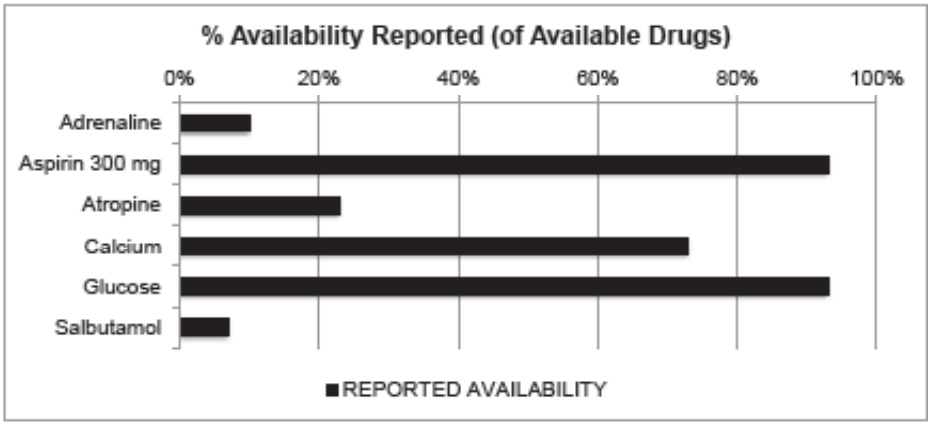


Fig 2. Surveyed provider-reported availability of medications *unavailable* at the clinic

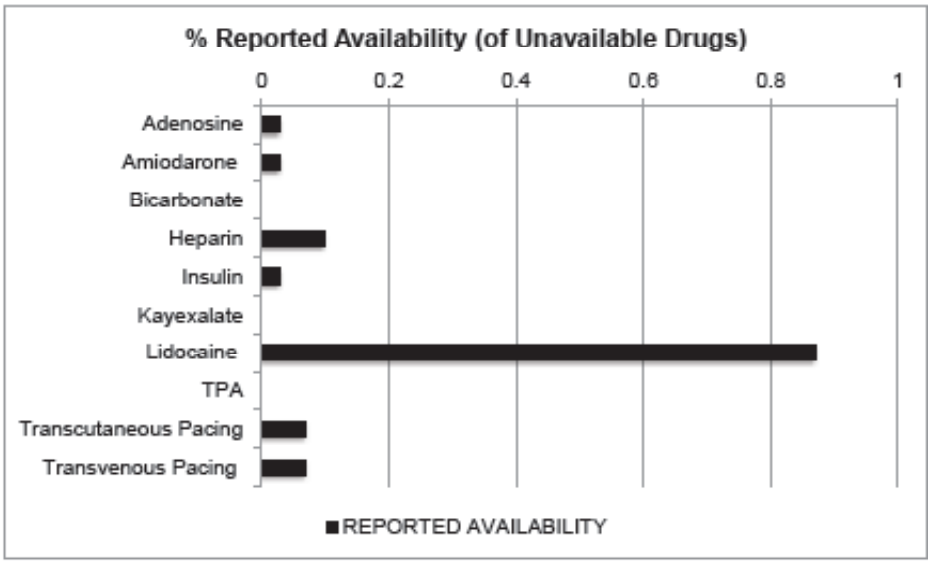
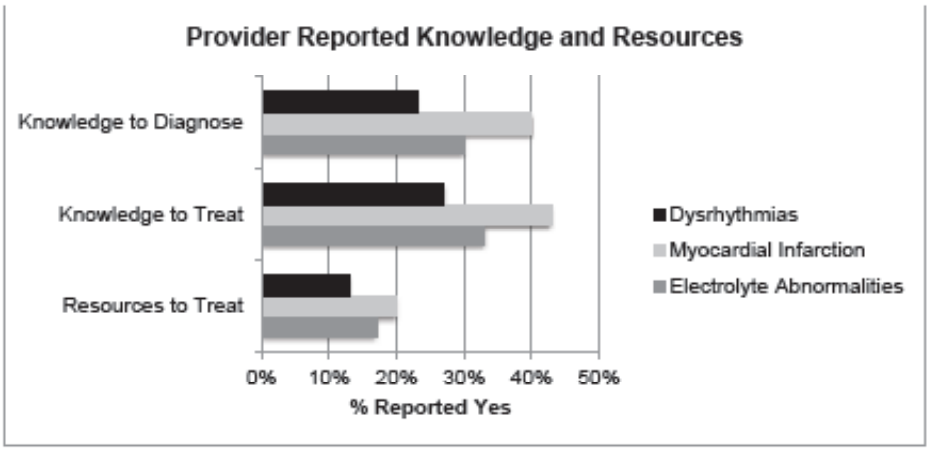


Fig 3. Reported knowledge and resources regarding common ECG diagnoses



training (43%).

This study also compared the provider-reported clinic availability of ECG-related drugs (medications commonly given for diagnoses related to ECG interpretation) with the actual availability of drugs at the clinic as reported by the supervising physician at the clinic. Figure 1 compares the list of available drugs within the clinic with the provider-reported availability. There was a wide variation in provider knowledge of availability from drug to drug. For example, aspirin and glucose were correctly identified as available drugs for the majority of providers (93% for both). Adrenaline and atropine were less familiar to providers and less frequently identified (10% and 23%, respectively), despite being available. On the other hand, treatments that were unavailable were mostly reported as unavailable, as shown in Figure 2. Providers knew that treatments such as adenosine, insulin and thrombolytics were not readily available (3%, 3% and 0% reported availability, respectively). Lidocaine was the only outlier with a reported availability of 87%.

As shown in Figure 3, certain cardiac diagnoses, such as myocardial infarction, are more familiar to providers in the clinic in terms of ECG diagnosis (40% provider comfort) and treatment (43% provider comfort) than other pathologies such as dysrhythmia diagnosis (23% provider comfort) and treatment (27% provider comfort). The resources that are available to treat ECG-based diagnoses are reported as low in all groups. Figure 3 also shows the percentages of provider-reported resource availability.

Discussion

ECG is easy to perform, requires few resources and quickly renders life-saving information. While the gold standard of care may not be available in resource-poor settings, ECGs can still assist in making correct diagnoses. Prognosis and patient/family education are important aspects of care. The ability to give a family a definitive diagnosis was unanimously thought among the surveyed health providers to be a useful and powerful tool; ECG may enhance this capability. Furthermore, certain diagnoses, such as ischemic heart disease and arrhythmia may be recognized by ECG alone and provide patients with readily available and affordable preventative medications such as daily aspirin or blood pressure control. This study did not collect clinical data to describe the incidence of these findings, but existing population data suggests a high incidence of ischemic disease and arrhythmia.

Based on the survey analysis there are apparent discrepancies in what medications are available within the clinic and what providers report are available. Understandably, in a place where ECG is not yet universally used, medications—such as aspirin—that are given for diagnoses other than ECG-related diagnoses have a higher reported availability (93%) than those—such as atropine (23%) and adrenaline (10%)—that are only given for ECG-related diagnoses in the setting of significant heart rate abnormalities or cardiac instability. Interestingly, there is no list of all available drugs given to the providers. Obtainment of this list of medications for this study was time-intensive and involved discussion with multiple staff members. Different areas of the clinic (i.e. pediatric, adult, obstetrics, surgical) also might have different familiarity with and frequency of use of different medications based on their patient population and common ailments. The survey did not require specification of the clinical specialty, but it would be interesting to include this in future studies. Intriguingly, providers in the study reported a high degree of comfort with the diagnosis and treatment of myocardial infarction, and a high level of resources for treatment of these conditions, despite the poor availability of catheterization or thrombolytics. One possible reason for this may

"While the gold standard of care (e.g. catheterization for acute ST elevation MI or pacemaker placement for complete heart block) may not be available in resource-poor settings, Electrocardiograms (ECGs) may still assist in making correct diagnoses."

be that heart attack may be diagnosed based upon clinical presentation alone, which means a lot in a clinic without monitors and with minimal blood results. On the other hand, providers reported a lower level of comfort with the diagnosis and treatment of dysrhythmias and electrolyte disturbance, as well as lower availability of treatments for these conditions. However, patients with these diagnoses actually had more treatments available than did patients with myocardial infarction (heart attack): atropine, adrenaline, magnesium, potassium and calcium were all available. Based on our descriptive results as well as previous work,[9-12] implementing an education program to improve knowledge of ECG interpretation, subsequent patient treatment, available medications could prove beneficial.

Based on the reported findings from the survey and focus groups discussions (Figures 1-3), a training program on ECG interpretation and diagnosis would be well received and useful. About two-thirds of respondents found knowledge of ECGs useful (60%) and interesting (63%). Given these results, the implementation of an ECG training program for medics should aim to increase knowledge of ECG interpretation and treatment, as well as medications availability in clinic, treatment of arrhythmias (i.e. adenosine for symptomatic bradycardia, diltiazem or digoxin for atrial fibrillation), gold standard treatment and counseling of patients and family members. Based upon the data gathered in this study, one possible solution would be to hold training of supervisory clinicians with outside staff either in person or via telecast. The supervisors could be trained to then hold trainings with other staff, and to educate other staff about diagnoses and treatments most relevant to their specialty. Including gold standard treatments in the training would not only be helpful prognostically, but also for the purpose of familiarity with treatments as resources and available medications change over time.

While these findings provide information that may be useful in other similarly resourced locations, this needs assessment is specific to this clinic and therefore the curriculum would not necessarily be generalizable to other sites and recommendations should be used with caution. However, this is the first study of its kind to evaluate the needs and utility of ECG in a low-resou,rce setting; more work needs to be done in this area to further our knowledge and increase the meaningful use of ECG in the developing world.

Limitations

As portrayed in the media, access to medical care for refugees and migraThe study had a small number of participants and was conducted at only one clinical site. Therefore the results of this study are not generalizable to other populations or sites. Another limitation is that a language barrier among all staff allowed only supervisory medics and physicians who spoke English to participate. This sample of providers was subject to selection bias as they may have more baseline knowledge than other providers who could not participate due to a language barrier. Finally a reporter bias may have been introduced by the fact that the information gathered here was all self-reported.

Conclusion

This study concludes that despite limited treatment options in low-resource settings, ECG is a useful diagnostic and prognostic tool. Knowledge regarding ECG utility and interpretation is minimal in this setting; providers are particularly eager to learn the material through hands-on training, lectures with handouts and specific ECG case study examples. Further research regarding the utility of and education about ECG use in resource-limited settings is needed.

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Spectrum of Comorbid Conditions and Their Relationship to CD4 T-lymphocyte Counts in HIV-Infected Patients in Mbour, Senegal

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Background: Individuals infected with the human immunodeficiency virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) present with a broad spectrum of clinical conditions as a result of compromised immune systems. There is little data reflecting the clinical spectrum and prevalence of comorbid conditions among HIV/AIDS patients in Mbour, Senegal.

Objective: This study aims to describe the incidence of comorbidities affecting HIV/AIDS patients in Mbour and to examine the relationship between comorbidities and CD4 T-lymphocyte counts in this population.

Materials and Methods: We conducted a retrospective chart review of patients seeking care for HIV/AIDS at the Hospital of Mbour (n=426) between March 2005 and May 2014. CD4 counts at presentation and comorbid conditions were documented and analyzed to determine frequency of each condition in the population and the relationship between CD4 counts and clinical presentation of disease.

Results: The most common condition in patients with HIV/AIDS at presentation in Mbour is chronic diarrhea (30.7% of patients), followed by dermatitis (29.5%) and oral candidiasis (25.4%). Patients presenting with candida infection, dermatitis and diarrheal illness have significantly lower CD4 counts than those presenting without these conditions. Patients with CD4 counts below 200 cells/μL have a greater number of comorbidities than patients with higher CD4 values.

Conclusion: This study outlines the clinical profiles of patients presenting with HIV/AIDS at the Hospital of Mbour and correlates symptoms with CD4 counts. This data could be utilized clinically to promote community educational outreach for early detection of disease based on the most common presentation of HIV/AIDS in this patient population.

Introduction

The HIV/AIDS pandemic has been at the frontline of public health interest in sub-Saharan Africa for the past thirty years. Despite the global media's focus on the AIDS crisis, there are persistent barriers to the eradication of the disease in many regions. These barriers include increasing poverty and limited access to basic health care for many of the poor and middle income residents of African countries like Senegal.[1] AIDS activists have drawn attention to the global disparities in access to technologies for HIV prevention, testing and treatment as well as impediments to access to primary health care or other health related resources. While great strides have been made in areas of universal access to treatment, many disparities persist as obstacles to effective disease prevention and detection.[1]

In the 1980s, the Senegalese government was one of the first African governments to acknowledge the HIV/AIDS pandemic and began to aggressively address this issue through education campaigns and blood screening.[2] At this time, the government made a financial commitment to universal access to HIV/AIDS treatment. T Today these treatments are still offered free of charge, by there has been only a modest decrease in the prevalence of HIV/AIDS in Senegal: From 0.6% in 2005 to 0.5% in 2015.[2] The estimated number of individuals living with HIV in Senegal in 2015 was 46,000, with 1,600 new HIV infections over the past year and 2,200 AIDS related deaths over the past year.[3] Despite government subsidization of treatment, only 18,375 of the 46,000 (40%) individuals living with HIV were receiving antiretroviral treatment in 2015.[3] An estimated 36% percent of pregnant women living with HIV received antiretroviral treatment to prevent mother-to-child transmission in 2015.[3] These numbers reflect the discordance between the aims of the global health community in universal treatment access and the reality of antiretroviral treatment status of many individuals in Senegal. The reason for the failure of such treatment programs is unknown. It should be noted that even though the prevalence of HIV/AIDS in Senegal has not decreased significantly since treatment reforms, it is still very low compared to the rest of Sub-Saharan Africa, where disease rates are as high as 28%.[4]

"Treatment 2015" is a Joint United Nations Program on HIV/AIDS (UNAIDS) initiative focusing on expediting progress towards universal treatment access. The initiative calls for innovative thinking in HIV counseling and encourages countries to establish national testing in order to facilitate earlier access to services.[5] This initiative acknowledges that the first step in increasing treatment efficacy involves increased knowledge of HIV status, which requires more widespread diagnostic efficiency. However, laboratory diagnosis of HIV in Mbour, Senegal is not always readily available due to the paucity of laboratories. In addition, such diagnostic testing must be paid for out of pocket. Given the financial and geographical barriers to laboratory testing for HIV status, recognizing HIV infection by its clinical manifestations in order to prompt a more thorough diagnosis and to ensure proper treatment when indicated remains essential.

The stage at which HIV is diagnosed is crucial, as earlier diagnoses are associated with improved patient survival, reduced direct care costs and lower rates of onward transmission.[6] Furthermore, early

and accurate recognition of HIV is vital to public health initiatives to eradicate the disease, as the risk of transmission increases eight to ten-fold during the acute phase of infection, defined as the six-month period following HIV acquisition when compared to the chronic phase.[6] Early initiation of treatment can reduce progression to AIDS.[7] However, clinical diagnosis of HIV-related conditions in the primary care setting is complex, as many of the presenting signs or symptoms associated with HIV are seen in individuals without HIV. Early HIV infection may manifest with symptoms including fever, fatigue, skin rash, diarrhea and weight loss.[8] Most symptoms of early infection are transient and relatively nonspecific. Moreover, even laboratory tests may not detect the immune system's antibody response during this phase.[9]

An important biological marker of HIV-related immunosuppression is the reduction of CD4 T-lymphocyte counts. The CD4 T-lymphocyte is an important coordinator of many immunologic functions. HIV selectively targets and infects CD4 T-lymphocytes, resulting in functional impairment and death of these cells. As the number of CD4 T-lymphocytes decreases, the risk and severity of comorbid conditions increases. Therefore, it is important to understand and recognize the specific comorbidities common to the HIV/AIDS population in Mbour in order to accurately diagnose and treat the disease as early as possible. A study performed in the United Kingdom by Damery et al. revealed that the conditions most strongly associated with subsequent HIV diagnosis were bacterial pneumonia, oral candidiasis, herpes zoster, weight loss, pyrexia of unknown origin and diarrhea.[10] An improved awareness of common disease manifestations specific to patients in Mbour, Senegal, may contribute to the efficacy of diagnosis and disease eradication in this region.

This study aims to outline the clinical spectrum of HIV-related disease at the Hospital of Mbour and to examine the relationship between presenting comorbidities and CD4 T-lymphocyte counts in this patient population. We hypothesized that CD4 counts would be lower in the patients presenting with comorbid disease when compared with patients without comorbid disease and that patients presenting with lower CD4 counts would display a greater number of comorbidities.

Table I: Frequency of comorbid conditions

Condition	Present		Absent	
	%	N	%	N
Candida of the mouth	25.4	107	74.6	314
Candida of the esophagus	12.6	53	87.4	368
Chronic diarrhea	30.7	129	69.3	291
Herpes	9.7	41	90.3	290
Pruriginous dermatitis	29.5	124	10.5	297
Sarcoma	0.24	1	99.8	420
Seborrheic dermatitis	0.71	3	99.3	417
Shingles	6.6	28	93.4	393
Tuberculosis	14.25	60	87.75	361

Method

Setting

This study took place at the Hospital of Mbour, a regional hospital in Senegal, West Africa. The Hospital of Mbour is a regional medical facility in the Thiès region of Senegal, which is located at the western border of the country. The Hospital of Mbour serves an area of over 500,000 people, has approximately 80 inpatient beds, 29 maternity beds and 140 medical staff, as measured by the researcher and collaborating physician. The hospital complex provides both ambulatory and inpatient care, and is affiliated and administered by the University of Thiès Medical School. While there are several smaller medical facilities in the Thiès region, the Hospital of Mbour is the only regional hospital with a government-funded AIDS treatment program. The hospital participates in a medical exchange program, allowing students from the United States to learn from the caregivers and patients in Mbour. In exchange, physicians from The Hospital of Mbour visit a hospital in the United States. This study was completed by a medical student from the United States in collaboration with a physician from The Hospital of Mbour as a means of quantifying years of data from paper charts.

Sample

The sample includes all charts from patients who were diagnosed with HIV or AIDS between March 2005 and May 2014 and who received care at the hospital facility.

Measures

Information was collected regarding age, gender (male or female), marital status (married, divorced, or single), CD4 count at presentation and presence or absence of nine individual comorbidities: tuberculosis, candidiasis of the mouth (fungal infection of the oral membranes), candidiasis of the esophagus (fungal infection of the esophagus), pruritic dermatitis (skin lesions with intense itching), herpes zoster (viral infection causing shingles), herpes simplex (viral infection causing ulcers), Kaposi sarcoma (a rare cancer due to a subtype of the herpes virus), seborrheic dermatitis (skin condition causing scaly patches) and chronic diarrhea. These nine comorbidities were the conditions outlined by the HIV/AIDS-specific charts, which have been utilized by the Hospital of Mbour since March 2005. These charts were organized and implemented in an attempt to better consolidate and record information about the HIV/AIDS patients who were diagnosed and treated at the Hospital of Mbour. This study was approved by ethics review boards at the lead author's institution with a letter of permission and support from the Hospital of Mbour. The lead researcher, with assistance from the head of Internal Medicine and director of the HIV program, developed the chart abstraction protocol, performed the chart review, and interpreted the results. There was no direct patient contact specific to the study as only existing data were used in our analysis.

Analytical approach: Descriptive statistics were employed to describe the distribution of demographic and clinical factors. The mean and standard deviation are provided for continuous variables and the frequency and number of patients in each category are provided for discrete variables (Table I). The percentage of patients presenting with each of the comorbidities was analyzed and reported as frequency and number of patients (Table II).

A two-tailed independent sample t-test was employed to assess the average CD4 count of patients in relation to comorbidity status (Table III). CD4 was dichotomized as CD4 >200 cells/μL and CD4 <200 cells/μL, with the latter indicating AIDS defining illness. T-tests were used to examine the relationship between the quantitative sum of comorbidities for any individual and AIDS-defining illness (Table III).

Results

The sample analyzed in this study includes 426 patients who received treatment for HIV/AIDS at the Hospital of Mbour. Data was collected from the first day that the individuals became patients at the Hospital of Mbour. The average age of presentation is 41 years and the average CD4 count at presentation is 295.8 cells/μL. There are 296 (69.5%) female and 130 (30.5%) male patients. Of the patients with HIV/AIDS, 53 (15%) are single, 225 (63.6%) are married and 74 (20.9%) are divorced. There are 74 charts missing data on marital status.

Table I reflects the frequency of each comorbid condition. The most common condition in patients with HIV/AIDS at presentation was chronic diarrhea (30.7% of patients), followed by pruritic dermatitis (29.5%) and candida of the mouth (25.4%). N reflects the number of patients with each comorbidity. Some charts were missing data regarding the presence or absence of the comorbidities, resulting in

Table II: CD4 mean

Condition (cells/μL)	Present	Absent	p-value	t-value
Candida of the mouth	228.8	320.8	0.0035*	2.94
Candida of the esophagus	176.5	312.4	<0.0001*	5.42+
Chronic diarrhea	205.5	336.7	<0.0001*	5.31+
Herpes	259.4	299.9	0.399	0.84
Pruriginous dermatitis	229.9	324.9	0.0004*	3.58+
Sarcoma	—	—	—	—
Seborrheic dermatitis	—	—	—	—
Shingles	240.8	299.6	0.115	1.63+
Tuberculosis	252.6	301.6	0.128	1.54+

*: p<0.05 according to student's t-test

—: Only 1 case had Sarcoma and 3 had Seborrheic dermatitis and as a result, t-values could not be calculated

+: Results from t-test using Satterwaite correction for inequality in variance

Table III: CD4 count and presence of comorbid conditions

	CD4>200	CD4<200	p-value	t-value (DF)
Mean number of comorbidities	1.0517	1.4735	0.0033*	-2.96

*: p<0.05 according to t-test

an incomplete count in each category.

Table II lists the mean CD4 count for patients presenting with and without the nine comorbid conditions included in this study. Patients presenting with candida of the mouth, candida of the esophagus, pruritic dermatitis and chronic diarrhea had significantly lower CD4 counts than those presenting without these conditions.

Table III lists the mean number of comorbidities present in patients with CD4 counts above and below 200 cells/μL. Patients with CD4 counts below 200 cells/μL presented with an average of 1.4735 comorbid conditions, while patients with CD4 counts above 200 cells/μL presented with an average of 1.0517 comorbid conditions. This is a significant finding (p= 0.0033), indicating that lower CD4 counts are correlated with a greater number of comorbid conditions in this patient population.

We hypothesized that CD4 counts would be lower in the patients presenting with comorbid disease when compared with patients without comorbid disease. The results listed in Table II reveal that patients presenting with candida of the mouth and esophagus, pruritic dermatitis and chronic diarrhea had significantly lower CD4 counts than patients presenting without these comorbidities. We also hypothesized that patients presenting with lower CD4 counts would display a greater number of comorbidities. The results listed in Table III show that patients with CD4 counts below 200 cells/μL are inflicted with a greater number of comorbidities than patients with higher CD4 values.

Concluison and Discussion

These results give insight into the clinical profiles of the patients with HIV/AIDS at the Hospital of Mbour, information that may be used to improve early detection of HIV symptomatology within the community or in the primary care setting. Our findings outline the most common comorbidities that are present at the onset of HIV infection in this patient population, including chronic diarrhea, dermatitis and oral candidiasis. This data may be useful for illustrating the common clinical picture of a patient with HIV/AIDS in a resource-poor environment, where additional laboratory testing is not readily available and physical examination is the primary diagnostic tool. In addition, these conditions could serve as useful indicators that prompt patients experiencing such symptoms to seek appropriate diagnostic workup. Furthermore, they could also be utilized as a focus of educational outreach to encourage community members to seek care as soon as such symptoms arise.

A number of studies examining comorbid conditions in HIV/AIDS have found data consistent with our findings. A study by Ramphoma et al. revealed that at least 70% of the people living with HIV/AIDS in Lesotho presented with oral manifestations of HIV as the first sign of disease. The majority (91.3%) of these cases are oral candidiasis, while other lesions found include Kaposi's sarcoma and oral hairy leukoplakia.[11] Okoh et al. observed that orofacial lesions were among the earliest clinical manifestations of HIV infection in Nigerian women, with 57% of patients presenting with oral lesions. Of these, oral candidiasis was the most common, with 37.8% affected, followed by melanotic pigmentation and xerostomia.[12]

Additional studies have investigated the prevalence of head and neck, ocular and hematological manifestations of disease. A study by Tshifularo et al., describing HIV-infected patients in South Africa, revealed that the most common manifestations were adenoid hyperplasia, cervical lymphadenopathy and chronic suppurative otitis media.[13] Bekele et al. outlined the most common ocular manifestations of HIV/AIDS in Ethiopia and found that the overall prevalence of ocular manifestations was 25.3%, with keratoconjunctivitis sicca (dry eyes) being most common.[14] Munyazesa et al. found that 4.2% of HIV-positive Rwandan women studied had marked anemia (Hb <10.0 g/dl), while none of the HIV-negative women had any degree of anemia. The degree of anemia was highest in HIV-positive women with CD4 <200 cells/mm.[2,15]

Our study revealed that patients with dermatitis had significantly lower CD4 counts than those presenting without these conditions. Boonchai et al. observed that 75% of HIV patients in Thailand with popular pruritic eruption (PPE) had an advanced degree of immunosuppression with CD4 counts below 50mm.[2,16] PPE is characterized by chronic pruritis on the trunk and extremities not explained by other causes and is the most common cutaneous manifestation in HIV infected patients.[16] Our results

support the hypothesis that pruritis may be regarded as a cutaneous marker of advanced HIV infection and used to predict the CD4 count in these patients, determine need for treatment and monitor response to treatment.

Candida infection among our sample was similarly associated with lower CD4 counts. Badiane et al. quantified the prevalence of opportunistic fungal diseases in the general population in Senegal, indicating that conditions such as candidemia, invasive aspergillosis, mucormycosis and histoplasmosis are likely underestimated due to lack of clinical suspicion and diagnostic test availability.[17] The authors suggest that fungal opportunistic infections are likely more common than the data shows, with diagnosed cases representing only a small fraction of the disease burden. Badiane et al. demonstrated that over a period of a year, 90% of those with AIDS defined as having a CD4 count below 200 cells/μL develop oral candidiasis. Our results showed a 25.4% prevalence of oral candidiasis at the time of presentation, but are limited in predicting the point prevalence and overall prevalence of disease due to the design of the study.

The most common comorbid condition present in our sample was chronic diarrhea (30.7%) and patients presenting with diarrheal illness had decreased CD4 counts compared with patients without this comorbidity. Rubaihayo et al. reported chronic diarrhea as one of the most common complications of HIV in a study analyzing the effects of treatment on prevalence of diarrheal disease. The study demonstrated a decline in diarrhea prevalence from 12% in 2002 before highly active antiretroviral therapy (HAART) availability to 2% in 2013 with the advancement of HAART availability in Uganda.[18] This study addresses the major negative impact of chronic diarrhea on quality of life for patients infected with HIV and also points out the effectiveness of HAART on combating the comorbidities of HIV infection with a significant reduction in prevalence with the onset of increased access to therapy.

The massive global expansion of access to HIV treatment has been promising, with 9.7 million people receiving HAART in low and middle-income countries in 2012 compared with 300,000 in 2002.[19] However, there are geographical variations in this success. As of December 2012, at least 80% of individuals with HIV were not receiving therapy, with the most dramatic gaps in treatment occurring in Western and Central Africa.[20] Our study analyzed the prevalence of comorbidities among all patients presenting with HIV from 2005 to 2014. Further research could analyze variations in patterns of disease presentation with time to evaluate the effectiveness of HAART therapy in this particular region.

This study was limited in the use of retrospective chart review to obtain data. The charts used by the Hospital of Mbour for patients with HIV included areas for documentation of only the comorbid diseases listed in Table II, limiting the results of this study to focus on these specific conditions. There are a vast number of clinical events defined by the WHO for clinical staging and classification not listed in this study, including persistent fever, anemia, pneumocystis pneumonia, HIV encephalopathy and molluscum contagiosum infection.[19] Further research might include identification of common conditions not listed on the routine charts used at the Hospital of Mbour. Further collaboration with the Hospital of Mbour might focus on expanding the criteria used to diagnose HIV/AIDS based on clinical presentation.

An additional limitation of the present study concerns the use of data present at patient presentation to the Hospital of Mbour. Due to the limited access to hospital care for patients in rural regions of Senegal, it is difficult to confirm the exact point in disease progression in which the patients initiated care at the Hospital of Mbour. It is not known whether patients sought care immediately after the onset of concerning symptoms, or if disease had been present for months or years before the initial visit to the hospital.

Further research might focus on identifying barriers to obtaining laboratory testing in the initial stages of HIV diagnosis in order to facilitate earlier diagnosis and better diagnostic outcomes. In addition, outreach programs focusing on educating members of the community about the common symptoms of HIV/AIDS may be implemented as a means of increasing the number of patients who are recognized and treated at early stages of disease.

A study by Lewden et al. that aimed to describe the causes of mortality in HIV-positive adults hospitalized in West Africa found that the most frequent fatal diseases were tuberculosis (36%), cerebral toxoplasmosis (10%) and cryptococcus (9%).[19] The study concluded that sustained efforts are needed to optimize earlier diagnosis of HIV infection and initiation of treatment. A goal of the present study is to expand the understanding of clinical presentations to enhance early diagnosis of HIV.

The results of this study reveal that the most common condition in patients with HIV/AIDS at presentation in Mbour is chronic diarrhea (30.7% of patients), followed by dermatitis (29.5%) and oral candidiasis (25.4%). Patients presenting with candida infection, dermatitis and diarrheal illness have significantly lower CD4 counts than those presenting without these conditions and patients with CD4 counts below 200 cells/μL present with a greater number of comorbidities than patients with higher CD4 values.

With very little existing data on the clinical presentation of HIV/AIDS patients in Mbour and Senegal as a whole, it is our hope that this study will increase the pool of available knowledge on this subject. In addition, the clinical comorbidities discussed in this study may be used as an indicator of disease to prompt patients to seek diagnostic workup for earlier detection of disease.

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Depression, Substance Abuse and Antiretroviral Non-adherence Among Adults with HIV in Care at the Clínica de Familia in La Romana, Dominican Republic

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Background: People living with HIV/AIDS (PLWHA) are more likely to experience a psychiatric disorder in their lifetime when compared to the general population. This can greatly affect adherence to the centerpiece of HIV treatment, antiretroviral therapy (ART), and the course that the illness can take. Depression and substance use are the two most common psychiatric disorders in PLWHA. This cross-sectional study examined rates of depression, substance use, adherence to ART and HIV biomarkers on a sample of HIV-positive patients serviced by a general medical clinic, Clinica de Familia La Romana (CFLR) in the Dominican Republic (DR).

Methods: A cross-sectional, questionnaire-based study was conducted in a clinic with a special program for PLWHA in La Romana, DR, over four weeks in Fall 2015. The questionnaire included demographic information and scales for assessing adherence, depression and substance use: the Morisky Medication Adherence Scale (MMAS-4), Patient Health Questionnaire-2 and -9 (PHQ-2 and -9) and CAGE-AID, respectively. Open-ended, exploratory questions on the experience of living with HIV/AIDS were posed to every fourth or fifth participant. Additionally, two important biomarkers for measuring HIV progression and severity, CD4 cell counts and HIV-RNA viral loads (most recent value within the last six months), were extracted from the medical chart. Data analysis was carried out using the Statistical Package of Social Sciences (SPSS) software.

Results: 89 participants were involved in the study. The mean age was 40.0 years old (SD 10.9) with an almost equal distribution of women and men; two participants self-identified as transgender. 80 participants (89.9%) scored positively on the PHQ-2, which means they met at least one of the two major criteria for depression: loss of interest in activities and depressed mood. The mean PHQ-9 for those who scored positive on the PHQ-2 was 10.6 (SD 4.7; threshold of 10 for major depression). Those with good ART adherence had a mean PHQ-9 of 9.4 (SD 5.0) while the mean for those with poor ART adherence was 11.2 (SD: 4.4). 27 participants (30.3%) fit criterion for severe alcohol or drug use (> 2). Participants endorsing drug use in their lifetime used marijuana (n=8) and cocaine (n=5). Based on the MMAS-4, 41.3% of those on ART had good adherence (score=0), whereas 58.7% had poor adherence (score > 1). Dominican origin and the completion of at least primary school were associated with good adherence (p-value = 0.04 and p-value = 0.03, respectively). Being female was associated with increased PHQ-9 scores (p-value = 0.01) as well as undetectable viral loads (p-value = 0.03); being male was associated with increased alcohol or drug use (p-value < 0.01). In the exploratory questions, most individuals reported acquiring HIV from a spouse or known romantic partner and reported being diagnosed after personally falling ill or witnessing their partner do so. Major concerns were inability to find work, loneliness and fear of discrimination.

Conclusions: Depressive symptoms and substance use were common factors that impacted ART adherence in a sample of PLWHA treated at Clinica de Familia La Romana in the Dominican Republic. Using validated measures to implement screening for depression and substance use could help identify those requiring diagnosis and appropriate care within the constraints of this low-resource clinic.

Introduction

Considerable evidence suggests that the majority of HIV-infected individuals will experience a diagnosable psychiatric disorder in their lifetimes at five times the rate of the general population.[1,2] Depression and substance abuse are the most common mental disorders in people living with HIV/AIDS (PLWHA).[3,4,5,6] Individuals with HIV are twice as likely to be diagnosed with depression compared to HIV-negative individuals, and a third of all depressed patients have a co-occurring substance use disorder.[7,8] One possible explanation for this link is that these disorders share common biological and psychosocial origins, and that depression leads to self-medication with alcohol and other drugs.[1]

Untreated depression and substance use disorders in PLWHA are associated with increased sexual risk behaviors, decreased immune response, a more rapid HIV disease progression due to ART non-adherence and thus possible ART drug resistance. [9] Multiple risk factors for nonadherence exist in this population, including lack of energy or motivation, feelings of hopelessness and social isolation or changes in cognition.[10] These facts render the treatment of depression and substance use in PLWHA of utmost importance.[1] Indeed, it has been shown that successfully treating psychiatric comorbidities benefits HIV-treatment retention, antiretroviral therapy (ART) adherence, HIV-RNA viral suppression and ultimately community viral load (a population-based measure of HIV-infected individuals' concentration of HIV-1 RNA).[11,12,13]

The causes of depression in PLWHA are likely multifactorial and involve social, psychological and biological factors.[1] Some psychosocial risk factors for depression in PLWHA include being of female gender, previous history of depression, comorbid psychiatric issues (i.e. substance abuse, psychosis), HIV-related physical symptoms, psychosocial impairment, avoidance behavior, unemployment and financial distress.[1] Additionally many risk factors for HIV (i.e. those presented to men who have sex with men (MSM), sex workers and other vulnerable populations) make an individual subject to discrimination and other stressors that can contribute to depression even prior to an HIV diagnosis.[1] Possible biological risk factors for depression in PLWHA include the neurotropic characteristics of the virus (i.e. invasion of the central nervous system and subsequent brain disease) as well as potential inflammatory processes due to HIV.[14] HIV infects important cells in the central nervous system (CNS) that can contribute to cognitive impairment, a predisposing factor for depression. Similarly, the chronic nature of HIV promotes continued inflammation that over time destroys the tissue in the CNS and throughout the body.

PLWHA with depression initiate ART later in the infection compared to those without depressive disorders (i.e. those with depression initiate ART on lower CD4 cell counts, a marker of immune-compromise, and higher HIV-RNA viral loads).[15] They also adhere poorly to ART once initiated.[16] Pooled data from one meta-analysis found that the likelihood of achieving good ART adherence among those with depressive symptoms was 42% lower than those without, regardless of the country's income and study design.[17] Even at subclinical levels, symptoms of depression have been linked to poor ART adherence and worse HIV-related outcomes.[16,18] A systematic review found that seven out of nine studies evaluating the impact of antidepressant treatment on ART adherence found improvement in adherence when treating depression with antidepressants.[19]

Substance use is often comorbid with depression and presents its own complications. A substance-abusing individual is also more likely to engage in risk-taking behavior under the influence of drugs or alcohol, which may contribute to new HIV infections and overall community viral load.[20] In PLWHA, regardless of co-infection with hepatitis B or C, heavy drinking predicts end-stage disease and mortality.[21] Some studies suggest that this stems from compromised ART adherence under the influence of substances, while others have found that the increase in morbidity and mortality associated with heavy drinking in PLWHA is independent of adherence.[22]

Diagnosing and treating substance abuse in PLWHA may have multiple benefits beyond addressing substance use: improving depression, promoting consistent ART adherence and consequently potentially achieving HIV viral suppression.[23,24] Furthermore, treating substance use may help prevent additional risk taking behavior and decrease the number of new cases of HIV.

In summary, strict adherence to ART is critical for HIV treatment success. It promotes sustained HIV suppression, reduced risk of drug resistance and improved overall health, quality of life and survival. Strict ART adherence also decreases community viral load by reducing the risk of HIV transmission between individuals.[25] To achieve viral suppression, an HIV-infected individual must be aware of theirdiagnosis, engage in HIV medical care, remain in care, start ART and consistently adhere to ART.[11] Depression and substance abuse interfere with all of these globally.[26] Lack of resources, cultural explanations of psychiatric disorders, low health and mental health literacy, poor social supports, poverty, the need for secrecy (nondisclosure) of HIV serostatus, denial and HIV-related stigma further contribute to the limited screening, diagnosis and treatment of mental and substance use disorders.[24] According to the World Health Organization, more than 95% of PLWHA reside in low and middle-income countries where resources are limited and research onmental illness of PLWHA is scant.[27]

Among low and middle-income regions, the prevalence of HIV among adults in the Caribbean is nearly 1%, making it the next most affected region after sub-Saharan Africa. And within the Caribbean, the Dominican Republic and Haiti comprise close to 75% of the total burden of disease. Additionally, in 2004, the government of the Dominican Republic began a program for national provision of ART with recent estimates quoting coverage of the HIV-infected population at 80%.[28] Given the high burden of disease and the high rate of ART coverage, the Dominican Republic appears to be a valuable place for research on HIV and factors such as mental health that could influence adherence.

This cross-sectional study examined rates of depression, substance use, adherence to ART and HIV biomarkers and their associations on a sample of HIV-positive patients serviced by a general medical clinic, Clinica de Familia La Romana (CFLR), in La Romana, DR, a low-resource setting.

Methods

Setting and Participants

This study was conducted between September 28 and October 23, 2015 at Clínica de Familia La Romana (CFLR), a general medical clinic that provides HIV care and ART treatment to adults and children living with HIV in the DR. At the time of the study, CFLR was caring for over 1,600 adults with HIV/AIDS, 82.7% of whom were on ART.[29]

CFLR was chosen as the site because it has an established track record for research, has hosted a large number of graduate students for such endeavors and, perhaps more importantly, was interested in evaluating the mental health of its population in an effort to continue improving the care it provides.

Spanish-speaking HIV-positive patients age 18 years or older attending CFLR and able to provide oral or written consent were eligible for recruitment in this study. They were either identified by their medical providers, as were most, or self-referred.

Study Instruments

The 2-page questionnaire included widely used measures validated in Spanish and was administered by a Spanish-speaking fourth year medical student researcher.

The PRIME-MD Patient Health Questionnaires (PHQ-2 and PHQ-9) are 2 and 9-item depression screeners. The PHQ-2 asks about whether an individual has experienced either depressed mood or loss of interest in activities (anhedonia) over the past two weeks, which are necessary criteria for a diagnosis of depression. A positive response to either of the two PHQ-2 items warrants administration of the PHQ-9 to determine whether the individual meets criteria for major depression. Administering the PHQ-2 first saves time by selecting out those individuals unlikely meet depression criteria. The PHQ-9 incorporates and expands on the PHQ-2; it is a nine-item measure that evaluates the occurrence and frequency of nine depressive symptoms during the past two weeks. Scores range from zero to 27 with higher scores indicating greater depression severity. Scores greater than ten indicate major depression (sensitivity of 88% and specificity of 88%).[30,31]

The CAGE questionnaire adapted to include drugs (CAGE-AID) is a four-item screener for lifetime alcohol use and drugs other than alcohol. It is not a diagnostic tool. A "yes" to two or more of the four questions is considered clinically significant and indicates a potential substance use disorder that warrants further investigation.[32] Scores greater than one (sensitivity of 79% and specificity of 77%) or greater than two (sensitivity of 70% and specificity of 85%) indicate a positive screen.[33]

The Morisky Medication Adherence Scale (MMAS-4) is a four-item yes/no measure examining forgetfulness, carelessness, side effects and feeling better as factors interfering with adherence to a medication regimen.[34] Scores of greater than three indicate low adherence, of one to two medium adherence and of zero high adherence (sensitivity

81% and specificity 44%).[35]

Every fourth or fifth participant was asked a series of open-ended questions designed by the researchers, ranging from questions about quality of life with HIV to more specific questions about adherence difficulties. It was decided that not all participants would be asked these questions in order to minimize disruption to the clinic's workflow. Additionally, these questions were potentially destabilizing, and there was limited infrastructure in place to provide the amount of emotional and logistical support that may be required to someone in profound distress.

The most recent (within the last six months) CD4 cell counts and HIV-RNA viral load were also abstracted from the participant's medical record. These two biomarkers are the gold standard for measuring HIV progression and severity.[36] CD4 cells are white blood cells that fight infection. Since HIV directly attacks the CD4 cell and uses the machinery within the cell to multiply and spread throughout the body, low CD4 cell counts in the presence of HIV infection indicate poor management of the disease. CD4 cell counts below 200 in HIV-infected individuals indicate advanced disease known as AIDS. Similarly, HIV-RNA viral load refers to the number of HIV virus particles in the blood: the higher the viral load, the less controlled the virus. Therefore, just like lower CD4 cell counts, higher HIV-RNA viral load indicates poorly controlled disease.

The study was approved by the Columbia University Medical Center Institutional Review Board (CUMC IRB) and the Consejo Nacional de Bioética en Salud (CONABIOS) in the Dominican Republic. All study materials were available in English and Spanish.

Analysis

Data analysis was carried out using the SPSS 23 (Statistical Package of Social Science program, version 23). Analysis included independent t-tests, Chi-square, and non-parametric tests. The aim of the analysis was first to describe the participants and second to test the association between depression, ART adherence, HIV-RNA viral load and CD4 cell count, as well as gender, origin, education, years lived with HIV, disease status shared, alcohol use and/or drug use. A p-value of < 0.05 was considered statistically significant. Qualitative analyses for the open-ended questions were conducted manually using Microsoft Excel for Mac 2011, version 14.6.

Results

Questionnaires were completed by 89 participants. CD4 cell counts and HIV-RNA viral loads were available for 88 and 87 participants, respectively. Results are organized into tables and graphs (see Appendix). The statistically significant results are identified below and in the tables with their respective p-values.

Sample Characteristics (Table 1)

Sociodemographics

The mean age of participants was 40.0 years old (Range 18-64; SD 10.9) and they were almost evenly divided between men (44.9%) and women (52.8%). Two participants identified themselves as transgender; their data was included in all the quantitative analyses except for the gender-specific ones where a sample size of two was insufficient to provide meaningful results. The majority of participants reported themselves as Dominican (73.0%), while the remaining 27% identified as Haitian or Dominican-Haitian. About half of the sample (46.1%) had completed only elementary school, 4.5% middle school, 28.1% high school, 10.1% no schooling and 11.2% university.

HIV clinical information

More than half of the participants (55.1%) had lived with HIV/AIDS for less than five years, with most of them (78.7%) reporting disclosing their HIV serostatus to someone. Almost all (89.9%) were taking ART medications. The sample mean CD4 cell count and detectable HIV-RNA viral load were 373.7 (SD 253.0) and 94,351.0 (SD 226,025.0), respectively. 24participants (27.3%) had a CD4 cell count < 200 (i.e. laboratory AIDS diagnosis), while 34 (39.1%) had an HIV-RNA viral load < 20 copies/mL (undetectable).

Depression

80 participants (89.9%) scored positively on the PHQ-2, prompting the administration of the PHQ-9. The mean PHQ-9 was 10.6 (SD 4.7; threshold of 10 for major depression). The PHQ-9 is scored as follows: a score of five through nine represents mild depression, Ten through 19 moderate depression, and 20 or greater severe depression. Most participants fell into the category of mild (31.3%) or moderate depression (33.8%), and two participants (2.5%) met criteria for severe depression. Mild depression represents a PHQ-9 score of five through nine, moderate depression

Of those meeting the threshold for major depression (PHQ-9 > 10), 66.7% were women, 70.5% were Dominican and 90.9% had received some level of education, very much paralleling the survey population. Additionally, 32 of the 44 participants meeting the threshold (72.7%) had a CD4 cell count > 200, while only 17 (38.6%) had an undetectable HIV-RNA viral load.

Substance Use

Seventy-seven participants (86.5%) reported lifetime use of drugs or alcohol and the sample mean CAGE-AID score was 1.0. Twenty-seven participants (30.3%) fit criterion for severe alcohol or drug use (score > 2). Thirteen and a half percent (13.5%) endorsed no alcohol or drug use and 56.2% endorsed moderate alcohol or drug use. The participants endorsing drug use in their lifetime used marijuana (n=8) and cocaine (n=5). In those participants with a CD4 cell count > 200, none to moderate alcohol or drug use was reported in 68.7%; severe alcohol or drug use was reported in only 31.3%. Similarly, in those with an undetectable HIV-RNA viral load, 70.6% reported none to moderate alcohol or drug use, while only 29.4% met criteria for severe alcohol or drug use.

ART Medication Adherence

80 participants (89.9%) were on ART as part of their HIV treatment. Based on the MMAS-4 instrument, 41.3% of those on ART had good adherence (score=0), whereas 58.7% had poor adherence (score > 1).37 Of those with good ART adherence, more were women (56.3%) than men (43.8%), and more had disclosed their HIV serostatus to someone (72.7%) than had not. 26 of the 33 with good adherence (79.0%) had CD4 cell counts > 200 and 17 (51.5%) had an undetectable HIV-RNA viral load.

HIV Biomarkers

Because a CD4 cell count < 200 qualifies for a diagnosis of AIDS, we examined the characteristics of the healthier participants with CD4 cell counts > 200. In this cohort of 64 participants (62 for the gender analysis), 58.1% were women, 71.9% were Dominican, 89.1% had completed at least primary school and 79.7% had disclosed their HIV serostatus to someone.

Associations (Tables 1-3)

The two adherence behaviors had different mean PHQ-9 scores. Those with good ART adherence had a mean PHQ-9 of 9.4 (SD 5.0), while those with poor ART adherence had a mean of 11.2 (SD: 4.4).

Good ART adherence was associated with being Dominican: 84.8% of good adherents were Dominican, while only 15.2% were Haitian or Dominican-Haitian (p-value = 0.04). It was also linked to having completed at least primary school (p-value = 0.03).

Meeting the threshold for depression was connected to female gender (p-value = 0.01) and to the individual having disclosed his or her HIV serostatus to someone, with 88.6% of those meeting criteria having disclosed (p-value = 0.03).

Male gender was positively associated with alcohol or drug use (p-value < 0.01). Female gender and Dominican origin were associated with undetectable (suppressed) viral loads (p-value = 0.03 for both).

Additional information

For reasons stated in the Methods section, open-ended exploratory questions were asked of every fourth or fifth participant for a total of 17 participants. We were particularly interested in learning more about patient experiences living with HIV/AIDS and how life may or may not be different now, in addition to understanding the behaviors that promote excellent ART adherence and the barriers. The predominant mode of HIV acquisition reported was from a spouse or known romantic partner, with a large proportion of participants becoming aware of their diagnosis (i.e. getting tested) after personally getting sick or witnessing their partner get sick. The theme of turning a negative into a positive emerged; many commented that receiving the diagnosis of HIV encouraged them to make positive changes in their lives, like quitting smoking or drinking, becoming more religious and being more cautious in their sexual relationships.

It was common for the participants to report having been in denial immediately after diagnosis. However, most felt more in control of their illness at the time of the study, except one participant who specifically

mentioned that she wished she had "some other chronic illness, not HIV" because of the stigma and discrimination towards PLWHA. Feelings of isolation and hardship were frequently related to feeling obligated to "hide the diagnosis" from others, even if it had been disclosed to a close friend or family member, for fear of discrimination or being denied work.

The predominant theme regarding behavior promoting ART adherence was having a schedule or routine. The barriers, however, varied considerably and included side effects, emotions like "wanting to forget" or feeling alone and simply being too busy. Two participants reported "vicious cycles" of binge drinking while in treatment. Major concerns included loneliness, desire to go back to work and financial trouble.

Discussion

This cross-sectional study aimed to measure the prevalence of depression and substance use as well as explore the relationship between these illnesses, ART adherence and two HIV biomarkers in PLWHA receiving care at CFLR in La Romana, Dominican Republic. The results suggest that depression, substance use and ART non-adherence were common in PLWHA.

The largest barrier to excellent ART adherence in PLWHA was scheduling and a busy lifestyle. Interventions exist, butthe most effective ones are multi-faceted, long-term and require full buy-in from the patient.[38] Co-existing depression and/or substance use that remain untreated complicate these HIV efforts even more.

Adherence and depression affected each other; there was a difference in the mean depression scores when separated by adherence behavior. While the association in this study was not statistically significant, this relationship is strongly supported in the literature and worth noting. It suggests that an ART non-adherent HIV-positive individual is more likely to be depressed, or that depression may increase the likelihood of ART non-adherence in PLWHA, both of which are reasons that screening for depression in PLWHA is essential.[39]

Depression was also associated with an individual having disclosed their HIV serostatus. Cross-sectional studies on this issue disagree. Some have found that disclosure of HIV status is significantly and inversely related to depression, while others have found that disclosure is not protective against depressive symptoms. Some have found no association between the two. [40,41] There are many reasons why depression and serostatus disclosure could be connected here, including that the disclosure event was met with a negative response or that there was a perceived or real lessening of support post-disclosure. In fact, PLWHA in the DR may inflate internalized stigma (i.e. worsen negative internal attitudes about themselves) by unknowingly and/or falsely exaggerating perceived HIV-related stigmas that exist in the community.[42] A patient's feelings post-HIV serostatus disclosure and the specifics of the disclosure event warrant further attention.

Statistically significant gender differences also emerged. HIV-positive women were more at risk for depression than HIV-positive men; this aligns with the predominant literature on the subject as well as rates of depression in women versus men in the general population.[43] Possible explanations for the higher rate of depression in women include the burden born by women as the primary caretaker for family members (i.e. caring for others before caring for self), less education, single parenthood and social isolation (i.e. homemakers).[44,45] HIV-positive men, however, had greater issues with substance use. That men in general suffer more from substance abuse than do women is well-supported.[46,47,48] However, the role that HIV plays is complex. Substance use in HIV-positive men can pre- or post-date the acquisition of HIV and data changes with sexual orientation and sexual risk-taking behaviors.[49,50] Subjects were not asked about infection timeline, sexual orientation or behaviors; future research could examine these subjects, as they are known to influence prevention and treatment interventions.[41,51]

Lastly, the history of Haitian-Dominican relations on their shared island of Hispaniola is long, tragic and marked by violence. This has had significant psychological and socioeconomic ramifications for Haitians and even those of Haitian descent and undoubtedly affects health literacy and healthcare access and engagement.[52] Though conflict goes back centuries, many cite the 1937 massacre under Dominican dictator Trujillo as the start of the current, persistent tensions, where over 20,000 Haitians or Dominicans of Haitian descent were brutally massacred. To this day, Haitians continue to be subject to mistreatment including recent government rulings to strip hundreds of thousands of Haitian immigrants and their descendants of Dominican citizenship and threatening mass deportations.[53] The consequences of this history shone through in this study, as noted above, where country of origin played a strong role in adherence, CD4 cell count and HIV viral load. More specifically, Dominican origin was positively correlated with good adherence, and being Haitian or of Haitian descent correlated with lower CD4 cell counts and higher HIV-RNA viral loads, both of which indicate poor viral control and worse clinical statuses. The simple awareness among HIV medical providers and treatment centers of Haitian vulnerability has the potential to improve treatment of HIV in the Dominican Republic on both an individual and community level.

There were several limitations to this study. First, due to the small sample of convenience, results from this study are not generalizable. Second, because of the way the questions are worded (i.e. "have you ever") MMAS-4 and CAGE-AID data only capture lifetime and not current problems. And third, the fact that this study was conducted in a clinic does not account for a potentially large number of PLWHA who are not connected to healthcare services.

Conclusion and Future Research

In summary, this study in a low-resource setting emphasizes the knowledge that depression and substance use correlate with poor adherence and poor HIV biomarkers. Consistent screening of depressive symptoms, with the PHQ-9 or a similar instrument, and of drug and alcohol use, with the CAGE-AID or its equivalent, would be beneficial on many levels, including improving HIV management. [54] Ideally, PLWHA who screen positively for depression or substance abuse would be referred to mental health professionals for evaluation and treatment. The most effective scenario would be a collaborative care model, whereby a patient's HIV and psychiatric care are consolidated under one roof, making it easier for both types of health care providers to discuss a patient's barriers to treatment with more ease. Funding for such systems in resource-poor settings has not yet caught up, so the hope is that studies like ours that support the need for these interventions will continue to build a strong case for them.

Both depression and substance use disorders in PLWHA can be effectively treated using multiple treatment modalities including pharmacotherapy and psychological interventions (e.g. various psychotherapies, including cognitive behavioral, behavioral activation, interpersonal and motivational interviewing, etc.). [8,55] Psychotherapy is the mainstay of low-resource settings; however, if the funding is available, pharmacologic treatments are also useful for treating depression in PLWHA.[39] As a result of this and other research, CFLR is implementing a new antidepressant program in which providers have been trained to apply the PHQ-9, the Mini International Neuropsychiatric Interview and follow evidence-based algorithms for depression, which will include pharmacologic treatments.

Finally, a representative longitudinal study that collects data on the patients at multiple time points, as opposed to our one cross-section, or a clinical trial (i.e. randomizing PLWHA who screen positively for depression to a mental health intervention versus placebo and looking at changes in adherence patterns) could more rigorously examine the intersection of depression, substance use, demographics and HIV-related outcomes in this vulnerable population receiving care in a low-resource setting.

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Conflicts of Interest

Authors claim no conflict of interest.

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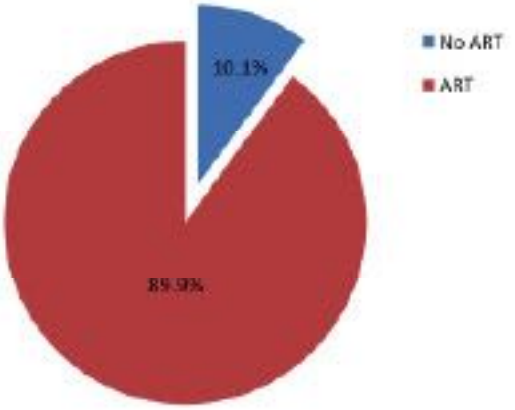
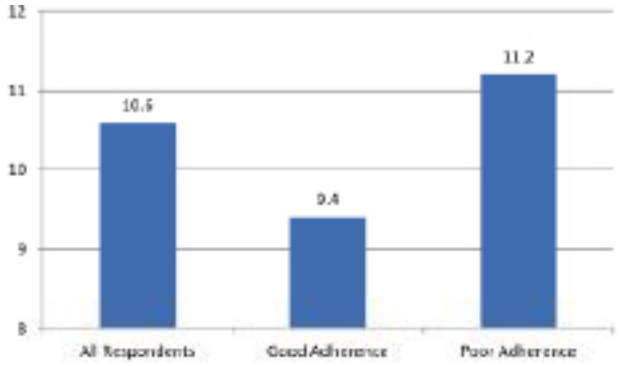
Appendix: Charts and Figures

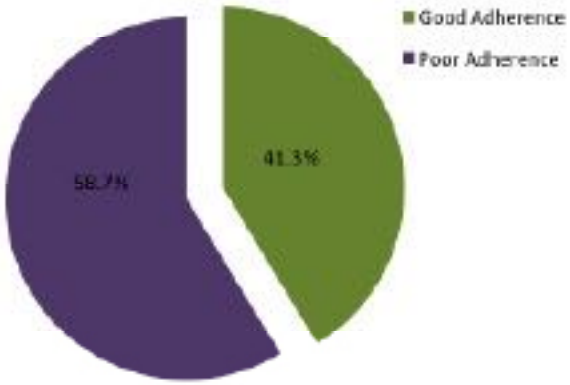
ART Adherence Rate



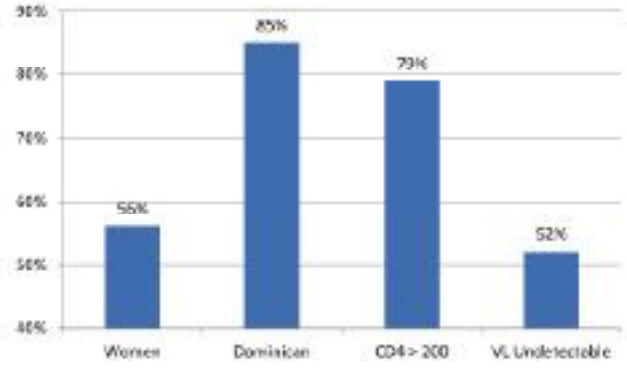
Mean PHQ-9 Score



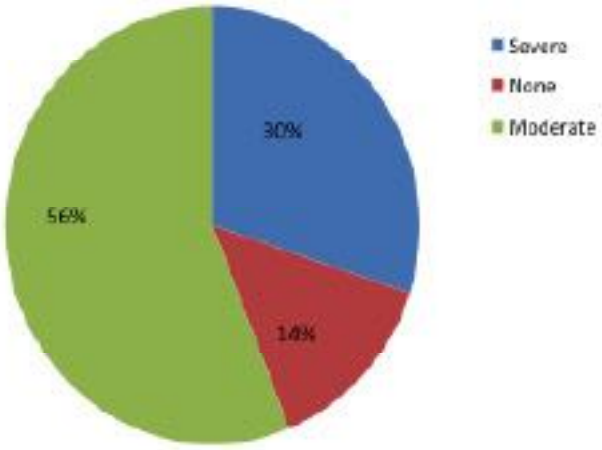
Within Adherence, Percent Good or Poor



Good Adherence



CAGE-AID



Prevalence and Risk Factors of Fatty Liver in Dehui City of Jilin Province of Northeastern China

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The prevalence of fatty liver disease (FLD), a chronic disorder that includes alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) ranges from 1% to 50% and varies with age, gender and occupation in different districts of China. Some studies have shown that FLD especially NAFLD, has a relationship with cardiac disease, metabolic syndrome, dyslipidemia and obesity. To determine the prevalence of FLD and related diseases in the Dehui City of Jilin Province in the Northeastern region of China, we surveyed the population of Dehui City of Jilin Province in China.

The objective of this study was to evaluate the prevalence of FLD in relation to different factors, such as age, location, occupations and educational levels, and analyze the risk factors of FLD.

The study sample was separated into three groups according to alcohol consumption: non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and suspected alcoholic liver disease (SALD) groups. All subjects (18-78 years) completed a standard questionnaire, physical examination and hepatic ultrasound examination. Multivariate logistic regression was used to screen risk factors of FLD.

The study indicated that the prevalence of FLD was 23.1%, stratified by NAFLD 14.5%, SALD 5.5% and ALD 3.0%. This survey showed a lower prevalence of hypertension between NAFLD and other groups (P<0.001). As alcohol consumption increased, the prevalence of FLD gradually decreased, when compared with NAFLD. The risk factors of FLD were hypertension, central obesity, alcohol consumption, dyslipidemia fasting blood glucose and being male.

Among groups of FLD, NAFLD has a higher prevalence in the Jilin Province of China. In China, elderly men with high educational levels working in mentally taxing fields are at a high risk of FLD. It is shown that hypertriglyceridemia is a very important risk factor to coronary heart disease, diabetes and hypertension. Generally, FLD was significantly associated with hypertension, drinking, high triglycerides and central obesity.

Introduction

Fatty liver disease (FLD), including alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), is a chronic disorder and is defined as lipid accumulation exceeding the normal range of five percent of wet liver weight. FLD encompasses a pathological spectrum consisting of hepatic steatosis, which is defined as the accumulation of fat in the liver; steatohepatitis occurs when steatosis becomes associated with inflammation, which can further progress to cirrhosis and hepatocellular carcinoma.[1] Currently, FLD has become a common problem both in developed and developing countries.[2] In China, the overall prevalence of NAFLD varies: 15.9% in the north-east of China, 17% in east China, 15% in south China and 41.6% in central China.[2,3,4] A study reported by Fan indicated that the community prevalence of NAFLD was about 15% in the more affluent regions of China.[5] It is 41.64% in a middle-class region and 36.49% in a lower class region.[6,7]

Historically, for FLD, most subjects were related to excessive alcoholic intake, but recently non-alcoholic precipitants of FLD have increasingly received more attention. Notwithstanding alcohol consumption, factors such as oxidative stress, mitochondrial dysfunction, insulin resistance (IR), immune dysregulation and adipokines are considered to play an important role in the pathogenesis of FLD.[8]

In recent years, the prevalence of FLD has increased dramatically in China due to alterations in lifestyle and dietary habits. Factors such as personal income, dietary habits and work surroundings have changed dramatically in the past 20 years. Meat and vegetable consumption has decreased for the majority of Chinese citizens as income has increased. Economic development has inevitably influenced the structure and habits of Chinese society; while there still is a great disparity between the richer and poorer classes, a growing middle class and high-income segment have emerged.[9]

Therefore, it is important to assess the epidemiological features of FLD in our country in order to facilitate its prevention and treatment. To date, there has only been one large population study from Jilin

Figure 1. Queries about drinking

Drinking Questionnaire	
1	Are you a drinker?
2	How often do you drink in a week and for how long?
3	Which type of drink do you consume most of the time?
4	Please write down your history of drinking of the last six months i.e. it should contain type of drink, degree of alcohol, volume and frequency of your drink.
5	Have you ever changed your habit of drinking? If yes, please write down your history of drinking before the change, it should contain type of drink, degree of alcohol, volume and frequency of your drink.
6	Have you ever quit drinking and why?
7	Have you other members in your family with the habit of drinking?

Province, located in northeast of China, published in 2008.[10] It was the result of a three-year investigation that focused on the overall prevalence of FLD and NAFLD. However, data from rural and city areas is still lacking, as well as data on ALD and SALD. This situation prompted our more detailed study of FLD epidemiology in the Jilin Province.

Subjects and Methods and Materials

Design

Approval from the institutional ethic committee of the First Hospital of Jilin University was obtained. This cross-sectional, population-based study was conducted in the city of Dehui, a city-level division of the Jilin Province in northeast China. Dehui has a population of 807,000, corresponding to 14 towns (urban) and 308 villages (rural). The economic status of the city is relatively affluent compared to other areas in Jilin Province. Therefore, to some extent, Dehui may be considered representative of the majority of the population of Jilin province and reflect the epidemiology of FLD there. The city has a moderate economic status among Jilin Province.

The sampling was random and multi-staged. Firstly, nine cities in Jilin Province were selected and numbered from one to nine. The city of Dehui was selected by simple randomization sampling (lottery method). In the second stage, nine villages and eleven towns were selected from 308 villages and 14 towns in the city of Dehui by random sampling, and in the third stage, cluster sampling was used in the areas selected above. The third stage was divided into two phases. In phase one, every participant was asked to participate in a questionnaire by door-to-door interviews. Phase two was of comprised of a physical examination and an ultrasound examination of the liver.

The sample size (N) was calculated based on a 10.0% prevalence (p) of fatty liver with a 1% uncertainty level (d), using the formula $N = t^2p(1-p)/d^2$ (where t^2 is defined by 95% confidence). We therefore estimated that this study would necessitate enrollment of 3,600 subjects. A total of 6,043 eligible subjects were selected from the district, all of whom should be permanent residents. Eventually, a total of 3,850 subjects accepted the questionnaire and physical and ultrasound examinations. A total of 3,815 subjects were included in this study, with 35 subjects being excluded due to their drinking history. Every participant signed the Informed Consent.

The selection criteria required the participants to be permanent residents of the city to control for sampling error. Before the study, a media-driven campaign was conducted in order to achieve a high level of participation. Risk screening for fatty liver was estimated by a questionnaire, via door-to-door interview. The survey was based on standardized interviews performed by trained health professionals. The survey data was collected and loaded using a personal computer within 24 hours after the interview. The questionnaire included self-reported age, gender, education, working hours, physical activity, smoking habits, family history of heart attack, hypertension, diabetes mellitus, alcohol consumption, awareness of arterial hypertension, drug prescription and two control measurements of systolic and diastolic blood pressure (BP). BP was measured by physicians before the interview under standard conditions (in an upright position, after about five minutes of resting time). Queries about drinking included seven items (Figure 1).

Ultrasound (US) examination of the liver was conducted by a total of 15 medical doctors of the hepatology department

Definitions and Preferred Cut-off Values

The diagnosis of FLD was based on ultrasonography, in accordance with the guidelines for diagnosis and treatment of non-alcoholic and alcoholic FLDs issued by Fatty Liver and Alcoholic Liver Disease Study Group of the Chinese Liver Disease Association.[11] These were adapted from the American Gastroenterological Association's medical position statement: nonalcoholic fatty liver disease from 2002.[12] Generally, the diagnosis of NAFLD and ALD was based on a combination of medical history, clinical symptoms, laboratory and ultrasound (US) findings. Viral hepatitis and other chronic liver diseases were excluded.

ALD was diagnosed when a subject fulfilled the FLD criteria and drank more than 40 g (male) or 20 g (female) alcohol per day over the course of five years. Suspected ALD (SALD) was defined when alcohol consumption was between 20-40 g (male) or 10-20

Table 1. Basic characteristics stratified by gender

Characteristic	Male (n = 1824)	Female (n = 1991)	P-value
Age	45.68±12.94	46.53±11.66	NS
Height	167.93±7.13	158.10±40.95	P <0.001
Weight	68.93±18.92	59.44±16.00	P <0.001
BMI	24.20±3.59	23.91±3.73	P <0.05
WC	83.78±10.83	79.21±10.44	P <0.001
SBP	130.52±20.34	128.34±22.17	P <0.001
DBP	85.00±12.99	81.73±12.80	P <0.001
FBG	5.24±1.35	4.96±1.31	P <0.001
CHOL	4.41±0.96	4.32±0.94	P <0.001
LDL	3.04±0.88	3.00±0.80	NS
TG	1.75±1.76	1.50±1.25	P <0.001
HDL	1.37±0.46	1.43±0.41	P <0.001

Table 2. Prevalence of ALD, SALD, NAFLD and FLD in different groups

Age	n	ALD	SALD	NAFLD	FLD
18-44	1222	2.70%*	5.89%	8.02%*	16.61%*
45-59	2022	3.51%†	5.73%	16.62%†	25.87%
≥60	571	2.10%	4.03%	21.02%	27.15%
Total	3815	3.04%	5.53%	14.52%	23.09%
P-value		P<0.001	P>0.05	P<0.001	P<0.001
Gender					
Male	1797	6.12%	11.41%	8.79%	26.32%
Female	2018	0.30%	0.30%	19.62%	20.22%
Total	3815	3.04%	5.53%	14.52%	23.09%
P-value		P<0.001	P<0.001	P<0.001	P<0.001
Area					
Rural area	2215	3.84%	7.18%	15.26%	26.28%
Urban area	1600	1.94%	3.25%	13.50%	18.69%
Total	3815	3.04%	5.53%	14.52%	23.09%
P-value		P=0.001	P<0.001	P>0.05	P<0.001
Occupation					
Mental work	1451	4.62%	7.58%	13.99%	26.19%
Physical work	2364	2.07%	4.27%	14.85%	21.19%
Total	3815	3.04%	5.53%	14.52%	23.09%
P-value		P<0.001	P<0.001	P>0.05	P<0.001
Education					
low-level	2770	2.17%	3.90%	15.78%	21.84%
high-level	1045	5.36%	9.86%	11.20%	26.41%
Total	3815	3.04%	5.53%	14.52%	23.09%
P-value		P<0.001	P<0.001	P<0.001	P=0.001
Monthly income					
low-level	2854	1.86%	3.54%	15.00%	20.39%
high-level	961	6.56%	11.45%	13.11%	31.11%
Total	3815	3.04%	5.53%	14.52%	23.09%
P-value		P<0.001	P<0.001	P>0.05	P<0.001

Compared with age group of 45-59: * P <0.05; ** P <0.001

Compared with age ≥ 60: † P <0.05.

g (female). NAFLD was diagnosed when alcohol consumption was less than these amounts.

Participants were classified as hypertensive, as defined by the World Health Organization (WHO) criteria, if their two control measurements of systolic blood pressure (SBP) were at or above 140 mmHg, or if their diastolic blood pressure (DBP) was at or above 90 mmHg, or if they were currently taking anti-hypertensive medications. Current cigarette smoking status was classified into three categories according to the number of cigarettes smoked per day: non-smokers, light smokers (1-20 cigarettes/day) and heavy smokers (>20 cigarettes/day).

For the dietary habit, the 'vegetable group' was defined as those eating more than 0.5 kilogram a day of vegetables or fruits and the 'meat group' was defined as those eating over 0.3 kilogram of meat a day.

Education level was classified into two groups: low-level and advanced. Low level of education group included no education, primary school, or middle school education (Grade One to Grade Nine). Advanced education levels included senior schools or colleges.[13]

Monthly incomes were classified into two categories: low-level (< 799 Yuan) and high-level (≥ 800 Yuan). In our study, professional occupations included farmers, workers, teachers, cadres, managers and self-employers. These occupations were separated into mental work and physical work performing groups. Brainwork group corresponded to teachers, cadres and managers, while physical work group includes farmers, factory workers and those who were self-employed.

We calculated the body mass indices (BMI=weight (kg)/height (m^2)). In accordance with the World Health Organization's Asian BMI criteria, overweight was defined as a BMI ≥ 23 kg/m^2 and obesity as BMI ≥ 25 kg/m^2. Central obesity was defined as waist circumference (WC) ≥ 90 cm in men and ≥80 cm in women.

With regard to alcohol consumption, participants were classified into three groups according to their estimated reported weekly intake: NAFLD (none), light (less than 40 g alcohol per day), moderate (40 – 80 g alcohol per day) and heavy (more than 80 g alcohol per day).

The levels of fasting blood glucose (FBG), total cholesterol (TC), high-density cholesterol (HDL-C), low-density cholesterol (LDL-C) and triglycerides (TG) were measured with a Synchron LX20 auto analyzer (Beckman Coulter, Brea, CA, USA). According to the Chinese guidelines on prevention and treatment of dyslipidemia in adults, hypercholesterolemia was defined as TC ≥ 5.18 mmol/L, high LDL-C as LDL-C ≥ 3.37 mmol/L, hypertriglyceridemia as TG ≥ 1.7 mmol/L and low HDL-C as HDL-C < 1.04 mmol/L.[14] Dyslipidemia was defined as the presence of one or more abnormal serum lipid concentrations. The ratio of TC to HDL-C (TC/HDL-C) was considered abnormal if the ratio was over 4.5.

Statistical Analysis

Descriptive statistics were utilized to analyze data consisting of numerical parameters: age, weight, BMI and BP, and all categorical parameters: physical activity, alcohol consumption, fat intake, cigarette smoking, family history of hypertension, educational level and occupation.

Table 3. Prevalence of diseases in NAFLD, SALD and ALD groups (n=3815)

	NAFLD (n=2700)	SALD (n=772)	ALD (n=343)
Hypertension	37.6%	43.5%**	48.7%**
Diabetes Mellitus	5.5%	3.9%	1.7%*
MS	18.9%	19.3%	22.4%
dyslipidemia	94.7%	93.0%†	97.1%
obesity	42.4%	26.7%†**	21.3%**

NAFLD is compared with SALD and ALD: * P <0.05; ** P <0.001

SALD is compared with ALD: † P <0.05.

To identify differences between the above-mentioned risk factors in the hypertensive and normotensive groups, Pearson χ^2-test and rank sum test were used. The χ^2-test was used for the rate and rank sum test use for measurement data. Relationships between risk factors were investigated by estimating the odds ratio (OR) using a logistic regression model. Separate univariate analyses were used to identify those variables associated with FLD. Because of interrelated between variables, multivariate logistic regression was performed to analysis the risk factors of FLD. Only probability values p<0.05 were considered to indicate statistical significance. The analysis software used was SPSS 18.0 for Windows.

"The main results of this qualitative study reveal that regardless of language barriers, cultural differences, inability to afford medical care and even absence ofdiplomatic relations, refugees in need of medical attention were provided care and UN, EU and WHO policies are upheld."

Results

Basic Characteristics Stratified by Gender

Anthropometric characteristics including height, weight, WC, SBP and DBP, blood pressure recordings and blood glucose levels of participants are presented in Table 1 to analyze significance between genders. There were no significant differences in the mean age and LDL-c between males and females. All the remaining variables were statistically significantly higher in men than in women with the exception of HDL, which was statistically significantly higher in women.

Overall Prevalence of FLD, NAFLD, ALD and SALD, and Their Relationship with Age, Gender and Way of Life

As shown in Table 2, 881 (23.1%) of the study's sample (3815) were diagnosed as having FLD. The overall prevalence of NAFLD, SALD and ALD was 554 (14.5%), 211 (5.5%) and 116 (3.0%), respectively. FLD prevalence was statistically associated with age (P<0.001), with no statistically significant increase over age 40 years (P>0.05). For ALD, age prevalence increased to the peak of 3.5% in the 44-59 years group but decreased over the age of 60 years (P<0.05); NAFLD prevalence increased with aging (P<0.001); the prevalence of SALD was not statistically different among age groups (P>0.05). When considering the subgroups of areas, type of work, educational levels and monthly income, ALD and SALD were statistically significantly (P<0.001). However, the prevalence of NAFLD was not statistically different between areas (P>0.05), occupations (P>0.05) and monthly income (P>0.05). The only statistically significant difference concerned educational levels (P<0.001).

Comparative Prevalence of Diseases Between NAFLD, SALD and ALD

Table 3 shows that the prevalence of hypertension in NAFLD was lower than in SALD (P<0.001) and ALD (P<0.001), without any statistically significant difference between SALD and ALD. As alcohol consumption increased, the prevalence of obesity gradually decreased (P<0.05), but there was no statistically significant difference in metabolic syndrome (MS) prevalence between the three groups. Dyslipidemia was significantly less prevalent in SALD than in NAFLD. Diabetes mellitus was statistically more prevalent in NAFLD than in ALD (P<0.05).

FLD and its Risk Factors

Table 4 shows the relationship between FLD and risk factors, determined by logistic regression. FLD was positively associated with male gender, hypertension, central obesity, drinking, hypercholesterolemia, high LDL-c, low HDL-c, high TG and high FBG. There was no correlation between FLD and education level.

Discussion

FLD—especially NAFLD—is the most common liver disease globally, with 3-24% of the general population affected.[15] Moreover, in the general population, 2-3% of fatty liver disease develops into liver cirrhosis and hepatocarcinoma.[16,17]

The prevalence of FLD is even higher in persons with type 2 diabetes (50%), obesity (76%) and morbid obesity (nearly 100%).[18] It was reported that that the prevalence of FLD in individuals with type 2 diabetes mellitus was 69.4% in Brazil and 55.8% in Tehran.[19,20] It is possible that different methods of sample selection, diagnostic criteria, dietary habits and life styles resulted in heterogeneous findings. For our purposes, we select the most accurate diagnostic criteria and take randomized methods to control the sample error, which may result in different findings. Different nations or racial groups and different dietary habits and lifestyles, such as large fat consumption, could also contribute to different findings.

Since China is a developing country, the lifestyle habits of the people are different from those living in more developed countries. Therefore, it is not unexpected that the prevalence of NAFLD in China is much lower (15.9%) than in developed countries. In accordance with reported data, this study showed that FLD was more frequent in males and increased with age.[21] However, some studies suggest that there may be a different relationship between NAFLD and age or gender.[22] Bedogni, et al. found that NAFLD prevalence increased with age in both genders and then significantly decreased for persons over 66 years. The variations between studies can be attributed to differences in social, cultural and environmental backgrounds among the study participants.

Our study shows that the prevalence of FLDF increased with age among residents of the Jilin Province, however, prevalence of FLD remained the same among age groups older than 40 years old. FLD prevalence was significantly higher in males than in females. The prevalence of NAFLD and ALD was higher in the north-east of China than in southern China. Regarding this last finding, there may be two explanations. First, the characteristically long winter in Northeast China may result in individuals partaking in fewer outdoor activities. Second, dietary habits could be another cause since anecdotally those in the north-east are reported to drink highly concentrated wine and consume more meat to keep warm. This study also showed that there is a summit rate of ALD at the 44-59 age group, but a decline in the 60 and up age group. This phenomenon could be explained as a result of type of occupation, but we fail to complete association with occupation in each age group.

This study also showed that the prevalence of hypertension in NAFLD was significantly lower than in SALD or ALD. This might be related to the known relationship between hypertension and drinking. Because drinking raises blood pressure to unhealthy levels, people with hypertension tend to drink less alcohol, which may result in fewer hypertension cases in people with NAFLD compared to SALD and ALD. As alcohol consumption increased, obesity decreased. The precise mechanisms underlying this relationship are not yet fully understood. Inhibition of normal *de novo* lipogenesis in the liver due to alcohol consumption might result in a lower prevalence of obesity. Multivariate logistic regression revealed that FLD was positively correlated with gender (males vs. females), hypertension, central obesity, alcohol consumption, hypercholesterolemia, high LDL-c, low HDL-c, high TG and FBG. No significant relationship with geographical areas or educational level was found. This contrasts with the results of a study conducted in Guangdong Province, which concluded that a high level of education and living in urban areas were found to be protective factors.[23] People with a low level of education in rural areas may be less aware of the risk of FLD and consequent unhealthy lifestyles may elevate the prevalence of FLD. In western countries, alcohol consumption, obesity and diabetes mellitus are the most common causes of FLD. Alcohol consumption has been reported to play an important role in contributing to ALD risk, but this study found that only 3.0% of the participants suffered from ALD.[24] Diabetes mellitus—a common disorder in developed countries—has become a severe problem in China due to alterations in lifestyles and dietary habits, including less physical activity and a diet with heavy consumption of fat and sugar. In this study, FBG was a major risk factor for FLD.

There are several limitations for this study: firstly, the cross-sectional nature of our study precludes us from determining cause-effect relationships. Secondly, we have to face the fact that our data were obtained from a few villages and towns in Dehui City of Jilin Province, so our results may not be generalizable to other localities. A potential concern is that we measured height, weight, waist circumference, fasting blood glucose, CHOL, triglycerides, HDL-c and LDL-c only once, which might have led to random error.

Conclusion

The prevalence of NAFLD was higher than SALD and ALD in Dehui City of Jilin Province of northeastern China. NAFLD was significantly associated with metabolic risk factors such as hypertension, high TG and central obesity, especially for males who regularly consumed alcohol.

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Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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Impact of Wheat Flour Folic Acid Fortification on Neural Tube Defects in Three Cities in Peru

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Objective: The purpose of this study was to assess the impact of fortification of wheat flour with folic acid on the prevalence of neural tube defects (NTDs) in three hospitals of the three natural regions of Peru by reducing anencephaly, spina bifida or encephalocele.

Methods: In 2012, a retrospective descriptive study of NTD prevalence in three public hospitals was conducted. The data corresponded to two periods: before (2001-2005) and after (2006-2010) implementing mandatory fortification of wheat flour with folic acid and other micronutrients in August 2005. Prevalence was calculated by dividing the total number of NTDs identified in the three hospitals by the total number of live newborns in the three hospitals (91.413) in 2001-2010. The 95% CI was calculated for NTD prevalence with the Poisson Test.

Results: A total of 101 newborns were found with an NTD, with mean gestational age of 37.7 weeks and mean weight of 2,808.6 grams. The prevalence of NTDs in the pre-fortification period was 12.1 per 10,000 live births and 10.1 per 10,000 live births in the post-fortification period. Pre- and post-NTD prevalences (per 10,000 live births) were 16.6 and 15.9 in Ayacucho, 12.3 and 10.1 in Tacna and 8.0 and 4.9 in Iquitos. Only the prevalence of spina bifida had a statistically significant reduction of 3.7 per 10,000 live births (p <0.05).

Conclusions: The implementation of wheat flour fortification with folic acid helped reduce the prevalence of NTDs in 2 per 10,000 NB, suggesting a positive impact of the intervention in the three study hospitals.

Introduction

In Latin American countries where infant mortality has declined to below 50 per 1,000 live births, congenital anomalies are the second or third cause of infant mortality, and therefore are a significant public health problem.[1] In Costa Rica, for example, neural tube defects (NTDs) are the second-leading cause of infant mortality.[2] Although in Peru infant mortality has been declined in recent years to 17 per 1000 live births, there are no specific data on morbidity and mortality by NTDs. NTDs are incurable birth defects that occur between the second and fifth weeks of embryonic development.[3,4] NTDs, such as anencephaly, spina bifida, encephalocele and others represent 85% of all central nervous system malformations.[5,6,7] Spina bifida occurs in 50% of cases of NTDs, anencephaly in 40% and encephalocele in 10%.[8] Anencephaly is fatal at or within a few hours of birth; spina bifida causes children to be paraplegic, develop hydrocephalus and suffer gastrointestinal and genitourinary problems. Since NTDs are incurable, prevention is the best option.

Although many factors (e.g. environmental, nutritional, genetic and ethnic) influence the occurrence of an NTD, the effect of other factors remains unknown. There is an increased need of folate during embryogenesis, growth and fetal development in the first months of gestation for the synthesis of nucleic acids and proteins.[9,10] As NTDs are associated with maternal folic acid insufficiency during pregnancy, strategies using folates attempt to prevent micronutrient deficiencies in the population and help prevent birth defects such as NTDs.[11,12,13] Regarding folic acid, Peru issued a law to fortify wheat flour with folic acid and other micronutrients. Under the initiative of Peruvian National Institutes of Health and the Ministry of Health, the government of Peru promoted Law 28314. It then approved the mandatory fortification of wheat flour with 1.2 mg of folic acid, iron and other micronutrients per kilogram. On August 4, 2005 regulations were formalized, with expected fortification implementation to be at 100% in one year.

Unlike other countries, where studies were conducted prior to the fortification of wheat flour to obtain a folic acid baseline, this did not occur in Peru. Without a folic acid baseline, direct quantification of the impact of the fortification on NTDs was not possible. As a way to measure the impact of the intervention in Peru, studies measuring the prevalence of NTDs before and after fortification were conducted in the National Maternal and Perinatal Institute in the Peruvian capital, Lima.[14,15] Although those studies demonstrated the effectiveness of wheat flour with folic acid fortification in Lima, no other studies were done in the interior of the country in order to measure its impact.

On the basis that fortification of wheat flour with folic acid would reduce the risk of occurrence of births with NTDs, this study evaluated the impact of Peru's fortification program on NTDs in three main hospitals in three cities of the natural regions of Peru.[16]

Table No. 1. Characteristics of mothers of babies with neural tube defects in three cities of Peru; 2001-2010

Characteristics	N°	%
Maternal age		
Adolescent	16	15.8
Adult	60	59.4
Not reported	25	24.8
Education		
No education	1	1
Primary	19	18.8
Secondary	42	41.6
College	9	8.9
Not reported	30	29.7
Civil status		
Single	9	8.9
Married	12	11.9
Cohabitation	52	51.5
Not reported	28	27.7
Mother in stable relationship		
No	9	8.9
Yes	64	63.4
Not reported	28	27.7
Mother's occupation		
House wife	64	63.4
Working	11	10.9
Student	2	2
Not reported	24	23.8
Prenatal care		
No prenatal care	12	11.9
Prenatal care	43	42.6
Not reported	46	45.5
Four or more prenatal visits		
No	7	6.9
Yes	36	35.6
Not reported	58	57.4

Methods

A retrospective descriptive study of NTD prevalence in three hospitals from selected representatives' cities of natural regions of Peru was performed from July to December 2012. The prevalence of NTDs during two different periods (before implementation of Law 28314, and after) were calculated, with 2001-2005 representing the period before and 2006-2010 representing the period after fortification. Hospitals from which the information was obtained corresponded to the public sector (Ministry of Health), with higher birth care coverage in the cities of Ayacucho in the Ayacucho Region (mountain range at 2,761 m.), Iquitos in the Loreto Region (jungle) and in the Tacna Region of Tacna (coast). Regions were selected for convenience.

The sample population was 91,413 live births, which corresponded to the total number of newborns in the three selected hospitals in the ten-year study period who met the requirement of complete medical history and diagnosis of an NTD. Characteristics of mothers of live births with NTDs in each hospital are presented in Table 1. Live births, by hospital, during the ten- year period are presented in Table 4.

While the objective was the measurement of the prevalence of NTDs, it was decided to review all medical records. We did not include stillbirths, abortions or pregnancy terminations for congenital anomalies.

Techniques and Instruments

To collect the data for live births with NTDs an ad hoc structured form was used. The data collected on the mother (?) included age, education, occupation, family background, folic acid supplementation during pregnancy and prenatal care; the data collected on the newborn included gestational age at birth, sex, weight, Apgar and type of NTD.

For the validity of the instrument for data collection, the opinion of five experts was obtained. A Kappa test was used to assess agreement for data collection between evaluators, and a high concordance was found.

Subsequently, health professionals from selected hospitals were

instructed to obtain data from medical records. The list of NTD cases from the Statistical Office of each hospital was requested. The medical records of the corresponding live newborns during the study period were requested to verify the diagnosis. In instances where a list was not available, other documents and the medical records were requested.

Ethical considerations

The study was evaluated and approved by the Research Council of the National University of San Marcos. An authorization from the Directorate General and the Ethics Committee of the hospitals where the study was conducted was obtained. A code was allocated to each of the cases included in the database. The first and last names of the newborn and the mother were not recorded.

Statistical analysis

An exploratory analysis of quantitative variables to assess the normality of the data was performed finding a normal distribution. The qualitative variables were presented as frequencies, percentages, averages, standard deviations and confidence intervals through the Poisson test. The overall prevalence of NTDs was calculated before and after fortification, considering newborns with any NTD among total newborns in the period of observation. NTD prevalence was calculated per hospital for the three hospitals and according to the type of NTD. To evaluate whether the observed reduction was significant, the Z test was used (a difference in proportions during the pre-and post-fortification periods, and $p < 0.05$ was considered statistically significant. 95% CIs were calculated with the Poisson Test for all prevalences.

Results

The overall average age of the mothers was 24.9 years with standard deviation ± 6.3 years, ranging from 14 to 40 years. Other characteristics of mothers of live births with NTDs in the three hospitals are presented in Table 1, but approximately 25% of those data had not been recorded in the hospitals' medical history. It was found that the average gestational age was 37.7 weeks and the average weight 2.81 kilograms, both before and after fortification. Live births before and after fortification scored between 1 and 9 on the one-minute Apgar; Apgar scores at 5 minutes fluctuated between 1 and 10. Scores of 7 and above are generally normal, 4 to 6 fairly low, and 3 and below generally regarded as critically low. A low score on the one-minute test may show that the neonate requires medical attention.

Overall NTD prevalence for the three hospitals saw a decrease of 2 per 10,000 LB during the post-fortification period. One city of study, Ayacucho, had a higher prevalence of NTDs during the pre-fortification period with 16.6 per 10,000 LB, which reduced by 0.7 ($p > 0.05$) to 15.9 per 10,000 LB during the post-fortification period. Likewise in Iquitos, a 3-per-10,000 LB reduction in the prevalence between the two periods of study was found ($p > 0.05$). Other results for the pre- and post-fortification periods in other cities are presented in Table 2.

Comparing prevalence by type of NTD between the two periods, it was found that post-fortification prevalence of spina bifida reached 5.1 per 10,000 LB, representing a reduction by 3.7 per 10,000 LB. Prevalences of anencephaly and encephalocele were not reduced. Other results related to type of NTD for the pre- and post-fortification periods are presented in Table 3.

The number of births in all hospitals of study is presented in Table 4.Given the above strengths and limitations, the implications

"In Latin American countries where infant mortality has declined to below 50 per 1,000 live births, congenital anomalies are the second or third cause of infant mortality, and therefore are a significant public health problem."

of this study's findings are threefold and the authors offer a few recommendations of recourse such as filling data gaps and securing improved working conditions for immigrants, racialized persons and women in order to minimize the risk of MSDs. First, government financial support programs should be considered in order ensure adequate surveillance and data collection of musculoskeletal injuries that is stratified by gender, ethnicity and immigrant status. Secondly, the findings could warrant policy changes that would prioritize occupational health, allow for greater recognition of immigrant skills and experiences and introduce employment models that would in turn allow for increased flexibility to fit the needs of women workers. Finally, the issues presented should also be on the agenda of global public health research, as ignoring them will lead to the possibility of diminished occupational health of workers.

Discussion

Studies in Lima showed reduction of NTDs in the National Maternal Perinatal Institute of Lima after implementation of the fortification of wheat flour Law 28314 in Peru, but not in cities located on the coast, mountains and jungle of Peru, a gap which this study attempts to redress.[14,15,17] This difference may be due to a lack of uniformity in data collection in some hospitals or omission by coders and diagnoses made in-hospital and not included on discharge records. In addition, there is a lack of neonatologists, whose knowledge is needed for a good diagnosis. Therefore, we suggest that hospitals without neonatologists have guides that include photographs of various forms of NTDs to facilitate diagnosis by other health professionals.

Overall results show a decrease in the prevalence of NTDs by 2.0 per 10,000 LB during the pre and- post-fortification periods ($p = 0.184$). While these results are not statistically significant, our results

Table No. 2. Distribution of neural tube defects prevalence in three cities of Peru; 2001-2010

Region	Pre fortification					Post fortification					P value
	N° NTD	N° LB	Prevalence per 10000 LB	CI 95%		N° NTD	N° LB	Prevalence per 10000 LB	CI 95%		
Ayacucho	20	12014	16.6	(10.2;	25.7)	24	15085	15.9	(10.2;	23.7)	0.441
Tacna	20	16204	12.3	(7.5;	19.1)	18	17858	10.1	(6.0;	15.9)	0.267
Loreto	11	13833	8.0	(4.0;	14.2)	8	16419	4.9	(2.1;	9.6)	0.148
Total	51	42051	12.1	(9.0;	15.9)	50	49362	10.1	(7.5;	13.4)	0.184

Table No. 3. Distribution of neural tube defects by type in three cities of Peru; 2001-2010

NTD type	Pre fortification					Post fortification					P Value
	N° NTD	Prevalence per 10,000 LB	CI 95%			N° NTD	Prevalence per 10,000 LB	CI 95%			
Anencephaly	7	1,7	(0,4;	2,9)		16	3,2	(1,7;	4,8)		0,938
Encephalocele	7	1,7	(0,4;	2,9)		9	1,8	(0,6;	3,0)		0,572
Spina bifida	37	8,8	(6,0;	11,6)		25	5,1	(0,6;	3,0)		0,017

Table 4. Distribution of births in three cities of Peru*

Años	Tacna	Loreto	Ayacucho	Total
2001	2693	1974	2072	6739
2002	3185	2750	2194	8129
2003	3198	3198	2564	8960
2004	3449	3323	2260	9032
2005	3679	2588	2924	9191
2006	3526	3181	3153	9860
2007	3612	3440	2917	9969
2008	3532	2852	2869	9253
2009	3673	3511	3084	10268
2010	3515	3435	3062	10012

* Total of newborns in hospital

are consistent with those reported by Sanabria et al. in the National Maternal and Perinatal Institute in Peru, which indicate a significant decrease of NTDs by 4.9 per 10 000 LB during the two periods.[14,15] As we know, there are unknown causes of NTDs that could possibly have led to these nonsignificant changes.

There is an impact of wheat flour fortification with folic acid in different countries. Brazil showed a reduction by 2.1 per 10,000 LB.[18] Chile reported a 31% drop in the prevalence of NTDs after wheat flour fortification started with folic acid in the year 2000.[19,20,21] Argentina also saw a significant reduction in mortality from neural tube defects by 67.8% for spina bifida and 56% for anencephaly.[22] Costa Rica not only fortified wheat flour but also corn, rice and milk, and showed a reduction in NTDs by 39% in the third year of fortification, an early fortification effect.[23] Having observed no greater positive impact in Peru with the fortification recommended by Law 28314, authorities should think about folic acid fortification of other foods.

While the highest prevalence of NTDs was reported in Tacna,

on the coast, results from both pre- and post-fortification periods differ with those reported by Saldarriaga et al., who postulated a possible association between the occurrence of NTDs and living at higher altitudes of around 2,000 meters.[24] Such geography is seen in Ayacucho, located on the mountain range at 2,746 meters above sea level. In this context, Cook et al. reported a lower prevalence of folate deficiency in non-pregnant women of childbearing age, a situation attributed to the adequate intake of folate by eating foods that provide folic acid, such as ceviche, which is not consumed as much in the mountain range in Ayacucho.[25] It is noteworthy that in Loreto (jungle) and Tacna (coast), reduction of NTD prevalence was higher than in Ayacucho (mountain). This could be due to a lower intake of products derived from wheat flour in Ayacucho, as the city is the capital of one of the poorest regions of Peru. It could also be that in Ayacucho wheat flour has had an ineffective fortification level of micronutrients. Even though there is a national fortification mandate, monitoring and regulation of the mandate is not necessarily so enforced in other cities of the country as they are in the capital Lima. This situation may explain differences between findings in Lima, Iquitos, Tacna and Ayacucho.

By analyzing the NTD reduction according to type, it was observed in this study that there was a significant reduction in spina bifida ($p = 0.017$), but not encephalocele or anencephaly. Our results were consistent with those reported in Costa Rica, Chile and Canada.[22,2627] However, this was not observed in the study of Sanabria et al., where it was found that the prevalence for anencephaly decreased, going from 5.1 to 1.9 per 10 000 LB (95% CI 1.0, 2.8), post-fortification; in his study the decrease for spina bifida and encephalocele were not statistically significant.[15] We don't have any explanations for doubling anencephaly cases in our study, as reasons for the increased risk of anencephaly among Hispanic mothers are not well understood.[28] Our results on prevalence of encephalocele are different from other studies in which reduction was observed in spina bifida, anencephaly and encephalocele.[22,27,29] An explanation is required for the non-reduction of the prevalence of encephalocele as well.

Although some medical records with NTDs were not located during the study, the expected reduction of neural tube defects was not evident; this limitation could be related to poor information systems, registration and storage of medical records, as well as a smaller number of diagnoses of congenital malformations due to a lack of specialists in the country. It is known that there are limitations in Peru for meeting the Classification of Diseases ICD-10 of the World Health Organization, such as various forms of underreporting or a lack of neonatologists who are needed for a good diagnosis.[28] It is likely that further observation by health professionals in the post-intervention period could have contributed to a greater overall decrease in the prevalence anencephaly, encephalocele, spina bifida and the other types of NTDs.

Lower NTD prevalence can be attributed to regions where wheat flour product consumption is high. Article 14 of the regulations of Law No. 28314, which ordered the fortification of wheat flour with micronutrients, states: "the National Center for Food and Nutrition conduct studies to determine the availability, access and consumption wheat flour and its derivatives as well as for measuring the impact of the fortification program."[17] As this means nutritional surveillance, improved logging also involves the implementation of an epidemiological surveillance system for NTDs nationwide, which already exists in Costa Rica, Nicaragua, Chile and other countries. Monitoring of compliance with the fortification of wheat flour with folic acid inside the country by the National Center for Food and Nutrition in production centers is also important. It will help to significantly decrease the overall prevalence of all forms of NTDs in Peru, since the great benefits of the use of folic acid can lead to reducing the incidence up to 72% of NTDs according to Kramer.[30]

In conclusion, after the implementation of the fortification of wheat flour in Peru in time and places of study, the overall reduced prevalence of NTDs was statistically insignificant at 2 per 10,000 RN ($p > 0.05$), but the reduced prevalence of spina bifida was significant at 3.7 per 10,000 LB ($p < 0.05$).

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Adverse Events after Voluntary Medical Male Circumcision in Swaziland

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Background: The Luke Commission (TLC) provides comprehensive mobile healthcare in rural Swaziland, a country with a 26% prevalence of HIV. Voluntary medical male circumcision (VMMC) has been shown to reduce the rate of HIV transmission by 60%. Initial national guidelines have recommended circumcision for infants and HIV-negative men ages 15-24 but have not included recommendations for boys ages 60 days-ten years old. This study evaluated the safety of circumcision in younger boys and those with HIV.

Methods: Forceps-guided circumcision was performed under local block in 1,500 male patients. Incidence of adverse events (AEs)--infection, bleeding and dehiscence - was examined as a function of age, weight, HIV status and season.

Results: The AE rate was 2.1% (31/1500); boys age ≤ 12 had 2.0% (20/1022) compared to 2.3% (11/478) in patients age ≥ 13 (p=0.66). Patients ≤ 29kg had 2.4% (16/662) AE compared to 1.8% (15/838) in patients >30kg (p=0.40). HIV-positive patients had 0% (0/76) AE. 2.9% (10/343) of patients who underwent circumcision during the summer incurred wound dehiscences, compared to 1.6% (10/640) in the fall and 0% (0/517) in the winter [p=0.001].

Conclusions: The novel use of double povidone-iodine prep with close follow-up produced adverse event rates comparable to those reported in the literature, even in rural settings. Circumcising younger patients or HIV-positive males did not result in higher adverse event rates.

Introduction

For over a decade, research has shown the efficacy of circumcision as a method to help prevent the spread of HIV[1,2,3]. Studies report up to a 60% reduction of the risk of HIV infection[1,2,3,4]. Mathematical models have suggested that widespread implementation of a circumcision program in sub-Saharan Africa would eliminate two million new cases of HIV over the first ten years[5].

Voluntary Medical Male Circumcision (VMMC) has been shown to reduce the risk of HIV transmission through several mechanisms[6]. First, the mucosa and submucosa of the foreskin contain a dense population of T cells, macrophages and Langerhans' cells that are positive for the CD4 cell marker, the target of the HIV virus[7]. Second, circumcised individuals have fewer microabrasions secondary to trauma during sexual intercourse, reducing the transmission of blood-borne infections such as HIV[8]. Third, circumcision has been shown to decrease the occurrence of syphilis and gonorrhea, both of which are associated with higher rates of HIV infection[9,10]

Swaziland currently has the highest prevalence of HIV in the world, with over a quarter of its adult population (27% of 800,000 people ages 15-49) being HIV positive[11,12]. To combat this epidemic, the Swaziland Ministry of Health (MOH) began its VMMC program with guidelines recommending the procedure for all Swazi males ages 15-24 who had tested negative for HIV[13].

Data from the United States President's Emergency Plan for AIDS Relief (PEPFAR) indicate that 81,381 Swazi men have undergone VMMC between 2007-2015[14]. While TLC circumcises male patients of all ages who come to an outreach clinic for VMMC regardless of HIV status, staff found that boys under four years old were unable to cooperate for the procedure performed under local anesthetic penile block.

In the first six months of 2014, TLC performed the operation on male Swazis ranging from four to 80 years old[15].

In the first six months of 2014, TLC performed the operation on male Swazis ranging from four to 80 years of age.[15]

Swaziland's MOH published new guidelines in 2016 encouraging a two-phase scale up program for VMMC: the catch-up phase addressing male Swazis ages ten and 49, prioritizing those between ten and 24, and the sustainability phase establishing an early infant male circumcision (EIMC) program requiring circumcision within 60 days of birth (NERCHA, 2016).

The Luke Commission (TLC) is a healthcare organization that for 11 years has provided comprehensive healthcare services to Swaziland's rural population, which encompasses >70% of the country's population of 1,297,378. TLC is faith-based and has partnered with the United States government through PEPFAR and is supported by both the United States Agency for International Development and Swaziland's Ministry of Health (The Luke Commission, 2013). TLC introduced its voluntary medical male circumcision (VMMC) program when the importance of circumcision in the battle against HIV became apparent.

TLC reasoned that circumcising younger boys would provide increased protection throughout their active sexual lifetimes, thereby decreasing HIV transmission potential. They also believed that with support from elders, who were also invited to undergo the procedure, the social acceptance of VMMC would be greater. Lastly, TLC reasoned that circumcising both HIV positive and negative male Swazis would reduce the stigma associated with being turned away from the healthcare facility after a positive test, leading to subsequent unwillingness by others to pursue the procedure[15].

This study investigates the safety of TLC's policy of circumcising all male patients, regardless of age, weight, and HIV status, by

examining the adverse event rate between groups. TLC uses extensive methods to minimize the rate of adverse events (AE), including the povidone-iodine double prep technique, as well as meticulous post-procedural follow-up on all patients.

The Swazi Male Circumcision for HIV Prevention Clinical Protocol, which details a single sterile patient preparation with povidone-iodine solution[13]. Since many of TLC's patients have limited or no access to running water or soap, preoperative hygiene and postoperative wound care are significant obstacles. TLC has dealt with this issue by using a double prep procedure that goes beyond the government's required single prep[15].At TLC, a Swazi staff member first washes the patient with povidone-iodine from the nipple line to mid-thigh. The patient is then prepped with povidone-iodine solution using sterile technique and is draped by a nurse to ensure readiness for the surgical procedure. Another important part of TLC's standard procedure is to provide all patients with transportation back to the sites of their surgeries on postoperative day two. On postoperative day two and day seven, a TLC nurse also removes the bandage to examine the wound and check for signs of adverse events. TLC has a telephone hotline available at all times to address the needs of their patients[15]. This close follow-up ensures that complications can be addressed early.

After the surgical procedure was completed, patients were sent to the recovery room, usually for several hours, until they could urinate without difficulty. Adverse events were identified at any point in the process, including immediately postoperatively, on one of two follow-up days or later by phone. A TLC nurse performed follow-up visits on postoperative days two and seven when she returned to the community, removed bandages, and examined the incision and surrounding tissue to check the healing progress. Most (29/34 or 85%) adverse events were identified during one of the two follow-up visits[15].

Material and Methods

The Wright State University Institutional Review Board approved this study. TLC staff reviewed and tested the validity and reliability of all data files.

The study sample included all male patients who underwent circumcision at a TLC mobile outreach between January and June of 2014. Consent from the patient and, in the case of minors (under 18 years old,) from a parent, was obtained. Staff members collected information on age, weight, HIV/TB status and sexual history. After performing a focused history and physical examination, a nurse recorded this information on an internal TLC procedural checklist to be transcribed into the permanent medical record and entered into the electronic database used for this study.

We examined wound infection, disruption/dehiscence and excessive bleeding since these three AEs could be assessed objectively and were the most critical (i.e. requiring immediate medical attention). Other AEs proposed for consideration by the World Health Organization include pain, swelling, anesthesia reactions, penile damage, erectile dysfunction, scarring, torsion, excessive/insufficient skin removal and voiding problems.

Several of these AEs require long-term data collection that would not be possible until the child reaches adulthood.

A secondary analysis was also conducted to examine the seasonal variation of adverse events (bleeding, infection and dehiscence). We hypothesized that the rate of adverse events for VMMC would be low and that HIV positive patients or individuals under the age of 15 would have similar AE rates as compared to older or HIV negative patients. The study's findings will contribute to Swaziland's future policy decisions and recommendations for the performance of male circumcision.

The chi-squared test or Fisher's Exact Test (FET) was used for comparisons between two groups (age, weight, HIV status) or three groups (season) and adverse events (any AE, dehiscence, infection and/or bleeding). FET was used when 20% or mor e of the cross-tabulation cells had expected counts less than 5.00 or one or more cell(s) had an expected count less than 1.00. Inferences were made at the 0.05 level of significance with no corrections for multiple comparisons. Analyses were conducted using IBM SPSS Statistics 22.0.

Table 1: Risk factors for adverse events among 1500 circumcised males in Swaziland

Risk Factor	Total Adverse Events	Wound Dehiscence	Infection
Age			
12 or younger	20/1022 (2.0%)	12/1,022 (1.2%)	10/1,022 (1.0%)
13 or older	11/478 (2.3%)	8/478 (1.7%)	3/478 (0.6%)
	p=0.66	p=0.43	p=0.77
Weight			
29kg or lower	16/662 (2.4%)	11/662 (1.7%)	8/662 (1.2%)
30kg or higher	15/838 (1.8%)	9/838 (1.1%)	5/838 (0.6%)
	p=0.40	p=0.32	p=0.20
HIV Status			
Positive	0/76 (0%)	0/76 (0%)	0/76 (0%)
Negative	31/1424 (2.2%)	20/1424 (1.4%)	13/1424 (0.9%)
	p=0.40	p=0.62	p=1.00
Season			
Summer	10/343 (2.9%)	10/343 (2.9%)	1/343 (0.3%)
Fall	15/640 (2.3%)	10/640 (1.6%)	6/640 (0.9%)
Winter	6/517 (1.2%)	0/517 (0%)	6/517 (1.2%)
	p=0.17	p=0.001*	p=0.39
Totals	31/1500 (2.1%)*	20/1500 (1.33%)	13/1500 (0.87%)

*Twenty-eight patients had 1 AE and three patients had 2 AEs.
**Single episode of bleeding was identified during the fall in a 12 year old, 30kg patie
**For pairwise comparisons: Summer > Winter (p<0.001) and Summer>Fall (p=0.003)

Results

For the 1500 patients in the study, follow-up was 99.7% at two days and 98.4% at seven days. Overall, 34 adverse events were reported in 31 patients: 20 wound dehiscences, 13 infections and one patient with excessive bleeding. The adverse event rate for all patients was 2.1%.

Age

Table 1 shows that in total there were 20 AE incidences among patients 12 years of age or younger (2.0%), and patients 13 years of age or older had 11 AEs in 478 circumcisions (2.3%) [p = 0.66].

For patients ≤ 12 years old, 12/1022 (1.2%) had wound dehiscence, and in the group ≥ 13 years old, 8/478 (1.7%) patients experienced wound dehiscence (p=0.43). Of those in the ≤ 12 years old group, 10/1022 (1.0%) experienced wound infection, while 3/478 (0.6%) had wound infection in the ≥ 13 years old group (p=0.77). The one case of bleeding was in the ≤ 12 years old group.

Weight

Table 1 shows that patients ≤ 29kg had 16 AEs in 662 patients (2.4%) while patients ≥ 30kg had 15 AEs in 838 circumcisions (1.8%) [p=0.40].

For patients ≤29kg, 11/662 (1.7%) had wound dehiscence, and in the ≥30 kg group, 9/838 (1.1%) experienced wound dehiscence (p=0.32). Of those in the ≤29kg group, 8/662 (1.2%) had wound infection, while 5/838 (0.6%) had wound infection in the ≥30kg group (p=0.20). The one case of bleeding was in the ≥30kg group.

HIV Status

Table 1 shows that there were no AEs reported in 76 HIV-positive patients and 31 AEs in 1424 (2.2%) HIV-negative patients [p=0.40].

For the HIV positive group, no patient (0/76, 0%) had wound dehiscence while 20/1424 (1.4%) experienced wound dehiscence in the HIV negative group (p=0.62). The incidence of infection was 0% (0 of 76) for the HIV positive group and 0.9% (13 of 1424) for the HIV negative group (p=1.00). The patient with bleeding was in the HIV negative group.

Season of Procedure

While the incidence of AEs in winter (6 of 517 or 1.2%) was less than half that of summer (10 of 343 or 2.9%) and fall (15 of 640 or 2.3%), the difference was not significant (p=0.17) [Table 1]. Wound dehiscence occurred more frequently in summer (10 of 343 or 2.9%) and fall (10 of 640 or 1.6%) than in winter (0 of 517 or 0%) [p < 0.001 and 0.003, respectively].

Discussion

Previous Swaziland national guidelines have been directed towards older HIV negative patients[13]. These guidelines specified circumcising only HIV negative men over the age of 15; TLC's patient population is notably younger than the national average. A 2009 study found that the average onset of puberty was 10.5 years old in surrounding areas of Africa[17]. For our analysis age groups were separated at 12 years old to ensure that the older group was composed primarily of post-pubertal patients in case puberty contributed to increased adverse events. Research regarding the average age of puberty and sexual engagement is lacking in our study's geographical area, and a large portion of the patient population (ages 10-14) could be considered a high-risk group whose medical needs are often overlooked[18]. We found that age and HIV status were not related to adverse events – i.e. younger and HIV positive patients were not more likely to have adverse events.

Initially, Swaziland targeted ages 15-24 since they were at greatest risk of HIV infection[19]. On behalf of Swaziland's Ministry of Health (MOH), a 2016 study showed which age-at-circumcision groups benefited most in prevention of HIV and cost-effectiveness[20]. Kripke et al. sought to address whether circumcision was more effective and cost-efficient in certain age groups using mathematical models. They found that the greatest magnitude of impact is seen in young men ages 15-29 but boys ages 10-14 have the longest-term benefits both for themselves as well as all future sexual partners[21]. Based on these findings, the MOH implemented a "scaled up" circumcision program for males, with coverage of 50% for newborns, 80% for 10-29 year olds, and 55% for ages 30–34.

TLC does not perform circumcision for infants, an important part of Swaziland's VMMC scale up. Infant circumcision must be performed within 60 days of birth.

The rural population served by TLC does not have regular access to health care nor the financial resources to travel to a clinic, and since circumcision was previously not part of Swazi culture, homebirth attendants historically do not perform the procedure.

The research investigating whether circumcision prevents the spread of HIV from infected men to uninfected partners is currently inconclusive. Theoretically, the transmission rate should decrease for the same reasons established in previous reports, such as lack of a hospitable environment for the virus and decreased trauma during intercourse[7,10]. Although research has not yet established the effectiveness of circumcising HIV positive patients to reduce the spread of HIV, TLC changed its policy to include these patients in its VMMC program in the hope of limiting stigmatization associated with publicly verbalizing a person's HIV status by turning him away from the outreach[20]. Under the Swaziland Ministry of Health directive of circumcising only HIV negative males, both those confirmed as positive and those who do not seek HIV testing due to apprehension would not be circumcised. Our findings support TLC's protocol since it shows that there is no greater incidence of

"Countries where HIV is epidemic, such as Swaziland, benefit when evidence-based voluntary medical male circumcision programs are instituted."

adverse events in HIV positive patients who undergo VMMC.

Our finding of no difference in adverse events (wound dehiscence, infection and bleeding) between age groups supports TLC's decision to widen its age range for circumcision. Currently, the guidelines for prophylactic HIV circumcision in Swaziland do not include circumcision in patients 60 days to ten years old. Circumcision in boys before the initiation of sexual activity will provide increased protection throughout their active sexual lifetimes, decreasing HIV transmission potential. With the support from the traditional leadership of community elders, the willingness of parents to allow their sons to undergo VMMC rose from 28% to 48% [22].

The only AE difference in subgroups was the increase in wound dehiscence during the summer rainy season. While this result indicates that the best times of year for circumcision would be during cooler, dry months, the benefit of decreased transmission of HIV outweighs the harm of a minor surgical complication.

Several topics are worth further explanation and exploration. First, the analysis of adverse events by season was limited to six months within one year due to seasonal variations of temperature and precipitation. For example, traveling to rural mountainous areas on dirt roads is impossible during the rainy season. Impediments to travel are a common issue in healthcare delivery throughout Africa. A study in Ghana showed that in a similar environment straight-line distance to the nearest healthcare facility is much shorter than the actual travel time due to difficulties such as dirt roads, mountainous terrain or vehicle accessibility issues, which are aggravated during the rainy summer months[23].

Secondly, while the 2.9% incidence of dehiscence during the summer months was the highest among the seasons, this rate is still lower than rates in most other sub-Saharan studies. A systematic review reported rates between 0%-24%, including 0% (Nigeria), 1.7% (Kenya), 2.8% (Tanzania), 3.5% (Kenya), 3.7% (Uganda), 3.8% (South Africa), 11.2% (Nigeria/ Kenya), 20.2% (Nigeria) and 24.1% (Nigeria)[24]. Comparisons of AE rates among organizations are difficult since the definitions of adverse events are variable. TLC uses the World Health Organization (WHO) definitions. TLC's youngest patients are four years old, with the majority between 10-14 years. The studies within the meta-analysis that contained similar age groups (15-49 years old) were conducted in South Africa and two in Kenya[22, 24, 25,26]. They reported AE rates of 3.8%, 3.7%, 1.7%%, and 3.5%, respectively. Most studies were conducted in major hospitals in large cities. TLC's program differs in that mobile hospital outreaches travel into rural mountainous regions without electricity or running water and set up the clinic using generators and buckets of water driven to the site.

Third, of the eleven adverse events listed by the WHO, we chose the three that could be assessed objectively and were the most critical since they require immediate medical attention. For example, if an infection is identified, the wound must be drained and antibiotics initiated. A more complete understanding of adverse events especially in younger and smaller patients would require assessing the other eight adverse events (pain, swelling, anesthesia reactions, penile damage, erectile dysfunction, scarring, torsion, excessive/ insufficient skin removal and voiding problems) over a longer period of time and with more patients as the incidence is very low.

Fourth, we only have follow-up data for patients on days two and seven postoperatively. With Swaziland's challenging, mountainous terrain, as well as with other logistical matters such as limited personnel and resources, adverse events requiring long-term follow-up can be addressed using TLC's hotline, but routine data are not collected.

Concluions

In summary, we found that the combined adverse event rate for wound dehiscence, infection and bleeding among 1500 male Swaziland circumcision patients did not differ by age, weight or HIV status. While seasonal variation was found to be statistically significant, the slight increase in AE rate by season was not important clinically. We have provided support for The Luke Commission's circumcision policy, including circumcising younger, older, and HIV positive patients. TLC's adverse event rate of 2.1% is less thanthat of many other African circumcision programs and comparable to worldwide rates. Countries where HIV is epidemic, such as Swaziland, benefit when evidence-based voluntary medical male circumcision programs are instituted.

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Potential Role for Institutional Review Boards in Curbing Medical Voluntourism in Global Health at American Academic Centers

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Across disciplines, consensus exists that medical voluntourism (as practiced by US-based health care professionals and professionals-in-training) is of questionable benefit to overseas health care practitioners and systems. This concern stands in sharp distinction to the increasing quantity of US-based global health activities, widely deemed "voluntouristic." This laxity in standards runs counter to the high level of self-policing otherwise seen in medicine. Various degree programs and certificates have been either created or proposed with the aim of identifying those passionate about long-term global health work but these programs have ultimately failed to reduce the incidence of global health voluntourism. To address the persistent concern of voluntourism, Institutional Review Boards (IRBs) might perform the role of adjudicating the appropriateness of proposed global health work for US-based academic health care professionals. This role would ultimately not be punitive, but instead it would serve to support committed practitioners while critiquing those in need of additional oversight. Such a system would add work to an already overburdened IRB system and would require new forms of expertise from IRBs. Despite these anticipated challenges, there is a need for formal, institutionalized review of all global engagement at the level of the individual. IRBs could perform such a role in ethically consistent but flexible ways.

An Oft Repeated Conflation

I recently watched a TEDx talk given by my global health mentor, Dr. Sriram Shamasunder of the University of California, San Francisco. He spoke of his years of work as a doctor in global health settings, both within and outside the United States. The talk was a multi-disciplinary discussion about why the medical and non-medical suffering of some "matters" while the suffering of others is ignored or forgotten.[1] In years of in-country, long-term global health work, he explored the realities of clinical suffering in global health settings, showed acumen in medical anthropology and linguistics and referenced historical systems like colonization and their modern manifestations. This multidisciplinary approach allowed him to discuss how access to creating and maintaining a historical narrative can be intimately tied to health outcomes and human rights. This was not a talk that could have been given solely based on long distance interactions or knowledge of the academic literature. This talk could only be given by someone with years of work experience overseas, by someone who is one of the pioneers of making global health a viable career option for passionate U.S. based health care professionals and by someone who has founded a global health fellowship that recruits equally from applicants hailing from high and low resource settings. In short, it demonstrated years of daily commitment to global health. Like many people passionate about global health, I want to carry a similar level of commitment throughout my career.

After the TEDx talk, it was a common response for listeners to compare their two week volunteer vacation overseas to my mentor's experiences. This conflating of someone's days of annual commitment with true multi-disciplinary, justice-based praxis is not uncommon. This piece will refer to the sum of that lack of preparation, language skill, expertise and longitudinal planning rooted in privilege seen in such "voluntourist vacations" and similar activities as "medical voluntourism." In this essay, I will argue that it is important for overseas health practitioners and health care systems, global health as a discipline and US-based global health practitioners serious in their work as professionals to distinguish the global health voluntourist from serious global health practitioners like my mentor. The existing Institutional Review Board (IRB) structure is uniquely suited to perform the role of delineating these individuals for US academic center based global health professionals.

The Pervasiveness of US Global Health Opportunities: A Sign of Strength or a Symptom of Sickness?

Throughout this paper, voluntourism describes an activity for someone coming from a more privileged setting that is ostensibly helpful but ultimately beneficial largely and only for the privileged individual. Medical voluntourism will be used to describe medical work where local health care professionals and health systems do not benefit after the individual has left and where there is neither meaningful longitudinal, collaborative relationship nor quantifiable output like publications, posters, quality improvement activities or treatment protocols. While the term "medical voluntourism" will generally be applied to physician examples throughout this piece it can apply to all healthcare professionals.

The literature of disciplines like medicine, sociology and anthropology accepts as a well-established tenet that medical voluntourism is a worrisome trend.[2-19] At best, medical voluntourism is edifying for the US-based practitioner while minimally beneficial to the local residents and the local health care system and its professionals;[2,5,8,17-21] at worst, it is actively harmful.[2,4,6,8-10,12,16] Medical voluntourism has been implicated in creating redundant or inappropriate care while diverting patients from the established, local public health care system and weakening the very same by siphoning off critical local health care workforce.[2,6-10,12,16] Medical voluntourism

sometimes addresses both acute medical issues without sufficient support for possible emergencies and chronic medical issues without chronic care infrastructure in place.[2,5,7,8,11,16,17] In doing such work, medical voluntourism often serves to further entrench inequalities it supposedly hopes to address[8-10,12] leading to phenomenon like "internal brain drain".[8-10, 12, 22, 23]

If these observations are true, it behooves us to stop medical voluntourism. In a review of the literature, there is a shocking lack of meaningful long term follow-up regarding the effectiveness of medical voluntourism, perhaps because such work is not conceived of in the arena of the long term. Concerns about medical voluntourism are seeping into the mainstream media, alternative media and even blogs.[7, 8, 24, 25] When asked, Malawian and Guatemalan medical professionals noted some positive aspects to the presence of foreign health professionals—generally related to approachable personality types or addressment of educational shortcomings created by the nature of work as Guatemalan or Malawian health care professionals—but raised major cross-cultural concerns relating to patients and adapting to care settings and ultimately wondered if many physicians possessed self-serving motivations.[18, 20] This piece will not further recapitulate arguments on why medical voluntourism is problematic but will propose a possible system to check medical voluntourist activities. It will not discuss medical voluntourism outside of the health professions or prior to enrolment in medical school but will instead target global health practitioners.

Interest in global health continues to grow even as concerns about medical voluntourism mount in the literature.[17, 21, 26-28] As of 2008, approximately half of US medical schools advertised global health opportunities on their websites.[17] A passing interest in global health without further career intentions suffices to open opportunities for Americans.[29] This reality is problematic for two reasons: 1) those with a passing interest are most likely to be shunted towards medically voluntouristic activities and 2) the low bar of a passing interest demonstrates a laxity in standards that runs counter to specialization in the American medical education system. First, it will generally be easiest to place those with a passing interest into voluntouristic activities simply because of their nature as short-term commitments with minimal preparation or need for expertise. We have already discussed the multiple, cross-disciplinary concerns with voluntourism. Second, this laxity in standards is perplexing. Let us assume global health work is its own form of medical specialization. As with any other form of medical specialization in the US, a passing interest would rarely suffice to create opportunities. One must first demonstrate a serious commitment involving further education, skill acquisition, research interest and professional networking to cardiology or oncology. Only then do further opportunities blossom. Yet, someone with only passing interest in global health can find him/herself at the very front lines of global health work without making any such commitment. Global health too often is a field with minimal oversight compared to other medical specialties. This lack of oversight allows not only a host of inappropriate and misguided activities to happen but also to occur under the auspices of doing good.

How do we begin to address these worrisome trends and lax standards in medical voluntourism in global health? Can a unifying degree program bind global health together? This act itself is difficult because the term "global health" is nebulous, often meaning different things to different people or in different settings.[30,31] Like public health, global health is both its own area of expertise requiring specific, additional training and a general field able to cut across all medical specialties, though, unlike public health, it has not developed into a unique discipline but instead functions as a subdiscipline of many other disciplines in health care. Perhaps, like public health, an officially recognized degree program(s) is needed to allow for easier delineation of those with and without expertise and to serve as a pathway forward for serious, future global health professionals while dissuading voluntourists. The Diploma in Tropical Medicine and Hygiene (DTM&H) is one example with graduates doing key global health work all over the world. DTM&H programs generally are short, intensive classroom and clinical based courses with a focus on tropical medicine.[32] Nonetheless, in reviewing two online DTM&H programs' curricula (the Mahidol course in Thailand and the Gorgas course in Peru),[32,33] these programs focus on infectious diseases. In the case of the Gorgas course, since inception, one in five students has been an infectious disease doctor with infectious disease representing the subspecialty with the highest enrollment numbers.[34] This fact limits generalizability as the burden of noncommunicable disease steadily grows worldwide. Similarly, recent innovations like Wilderness Medicine or Disaster Preparedness are important steps forward in terms of specific training modalities. In the case of Disaster Preparedness training in the US, it is largely housed in Emergency Medicine,[35,36] and like the DTM&H to infectious disease, is most applicable to practitioners trained in the Emergency Department. It will be difficult to create a unifying Masters of Public Health or Masters of Population Health equivalent for global health. The field sprung up too quickly and too diffusely,[37] and is too far reaching to allow for such a solution.

"The literature of disciplines like medicine, sociology and anthropology accepts as a well-established tenet that medical voluntourism is a worrisome trend. At best, medical voluntourism is edifying for the US-based practitioner while minimally beneficial to the local residents and the local health care system and its professionals; at worst, it is actively harmful."

Others suggest global health board certification or competencies to organize and provide oversight to global health.[38,39] This idea is hard both philosophically and logistically.[40] As mentioned above, global health professionals have enough difficulty defining "global health;" one could imagine years of infighting about what does and does not belong as part of a certificate program or on an exam. In a field that is sometimes mired by partisanship and an almost colonialistic approach to divvying up spheres of foreign influence,[41] questions loom large about which present or future governing body or institution will administer said certificate or

test and how it will do so.

It appears previous degree programs do an excellent job of identifying committed global health professionals but are perhaps less successful at dissuading voluntourism. The critical task of dissuading the misguided but well-intentioned is an important step forward for our field and will require an oversight that cannot be rooted at the level of a governing body or unifying degree. As global health has taken on so many real and valuable manifestations at so many different US academic institutions,[19] such oversight must occur at the institutional level under a unifying set of guiding principles.

The Imperfect Case for IRBs

For US-based academic centers, the institution itself seems an appropriate location to place the locus of control for medical voluntourism. Larger oversight than this level would require the creation of a whole new bureaucracy, while smaller than this would be the current standard of policing this serious issue at the level of the individual. Most medical institutions already possess a diverse ethical body which meets regularly to determine the appropriateness of activities with clear ethical implications. This body is usually called the Institutional Review Board (IRB). IRBs can provide voluntourism oversight in a manner reminiscent to how research is vetted in the same setting.

IRBs already traffic in ethics, but only as ethics relates to research. Their development is intimately linked to the history of highly unethical research that was done not only by cruel regimes but also by well-intentioned scientists with tunnel vision for research quality who subsequently hurt human study participants.[42-45] While global health voluntourism is not as obvious harmful; as noted previously, its utility is very much in question. Global health professionals are reaching a crossroads similar to researchers faced after learning of chronic, untreated syphilis in the African American community during the Tuskegee Experiment. What must be done to build an oversight system that allows global health professionals to complete their work with independent verification of ethical conduct? As they do for research ethics, perhaps IRBs can help address the issue at the looming ethical crossroads before us: what can be done to stop global health work that is not properly planned by individuals without cultural or linguistic competency and no long-term plan to collaborate with existing health systems longitudinally?

IRBs are usually well connected to the medical campus research infrastructure and are already conscious of research work overseas. The international projects of which the IRB would be aware are often the strongest, best established and longest running international collaborations at an institution and, in many cases, are the only international projects whose worthiness had to be adjudicated by outside authorities, including international partners and funding mechanisms. This means IRBs not only have a sense for what is happening in the field but also what is possible given the institution's resources and expertise. In this way, IRBs could help coordinate global health professionals with overlapping work focuses, whether geographic or topical. Stories of global health colleagues happening upon another colleague from their same, US-based institution while working at their international site are not uncommon. While there is nothing intrinsically wrong with this event, it is a bit embarrassing and highlights the occasional isolation and lack of communication even among like-minded and similarly focused individuals. While the IRB likely cannot play a coordinating role, the IRB's existing knowledge base could at a minimum make these individuals aware of each other even if just through something like an online register whereby the IRB application itself prompts you concerning other work in your field or geographic region of interest and provides contact information.

IRBs also have the ability to apply unifying ethical principles on a case-by-case basis, as they already do in research work. This fact allows IRBs some limited flexibility. As more IRBs address the appropriateness of proposed/ongoing global health work, we would see the development of a *de facto* standard which all overseas work must clear to receive any IRB's blessing. Despite this *de facto* standard, the limited flexibility will be critically important for one specific group of global health professionals: those individuals looking to get established in the field.

Imagine two fourth-year medical students who want to go to Guatemala for four weeks. The IRB can differentiate between one student who has Spanish or indigenous language(s) fluency and who has made inroads establishing relationships with Guatemalan health professionals and another student who has not. The latter student would not be allowed to do a visiting rotation at another US-based medical center with this level of preparation and similarly would not be allowed to go to Guatemala. Similarly, we can imagine two final-year fellows nearing completion of specialization training who express a desire to go Malawi. One fellow has a track record of high quality projects and publications in another region of the world that are now completed, and expresses a desire to find a new overseas institutional home with which to collaborate long term. The other fellow has been to many overseas sites but has minimal evidence of substantive previous work. The first fellow has an established track record and should be given the opportunity to begin new work. The second fellow should be made aware of a pattern of voluntouristic behavior and should be held to a stringent standard prior to clearance for his/her work. The IRB would never be able to figure out who really wants to go on a sightseeing vacation and who wants to simply build their resume, but it could maintain the above standards.

It would be necessary to maintain a lower standard for new global health professionals, whereby it is easier for them to get clearance for their first work abroad. Not all these individuals will decide to pursue careers in global health. This lower standard would mean that a portion of global health work would not lead to productive long term collaborations, though the work that would be done would be more carefully thought out an appropriately vetted. This is a compromise that must be made so individuals can be allowed the opportunity to experience the field and make an informed career decision. However, one can imagine the standard becoming more stringent as one adjudicates more experienced global health professionals as in our examples above. In all of the above, the IRB could serve as a space for reflection about one's mission and its focus.

Global health is already a diverse, multidisciplinary field requiring competency in not only medicine but also social sciences, anthropology, history and linguistics. IRBs are already one of the few places on a medical campus where individuals with non-medical backgrounds play a pivotal role; in fact, IRBs cannot work without those individuals. As global health is contingent on the input of a multi-disciplinary team, IRBs are uniquely situated to be of service to global health.

What Would this Role for IRBs Practically Look Like?s.

Ultimately, the IRBs would play a similar role to the role they currently play in research. However, while traditionally the IRBs research work is a critique of a certain project, in this role the critique would be of the individual or small team. Even though this individual-level evaluation could be punitive, its ultimate goal would be to affirm people who do high quality global health work and help to thoughtfully critique individuals whose planning and collaboration needs work in an iterative process. The goal is not only to stop voluntourists but grant well-meaning individuals in danger of falling into voluntourism the best opportunity to avoid these pitfalls. Committed but inexperienced individuals willing to work with the IRB's critiques could be plugged into established mentorship and collaborations at an institution, where their energies can be redirected in more positive directions.

The logistics of the process would likely follow a similar pattern. Each individual or small group would likely need to submit an up-to-date CV and short statement of intent to the IRB. This would serve as an initial screen and lend itself to a formal, face-to-face interview. The interview would be a critical portion of adjudicating the individual or small group. Each individual would likely be interviewed in a two-part fashion. During the first section, he or she would be asked at some length about previous experience overseas through the use of his or her CV or passport. This section would serve to establish each individual's level and pattern of previous global health work to best determine how most fairly to assess his or her application. This section would also most likely serve as the screen for concerns related to previous voluntouristic behaviors. Multiple short trips without longitudinal work and a lack of quantitative output would serve as red flags to the IRB. In the second portion, the individual's proposed

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current activity would be scrutinized with the lens and necessary intensity established by the first part of the interview. Language fluency or competence could also be assessed at this time. To this end, each IRB would make use of certain general principles that could be broadly applied to each individual. Follow-up interviews could be performed in an as needed fashion as part of an iterative process. As noted earlier, there would be no "one size fits all" approach but rather a more generous inclusion of individuals new to global health work with more stringent criteria for those with previous experience, especially voluntouristic experience. The following criteria could serve as a baseline which each IRB could use to create its own rubric regarding individuals and small groups:

Plan

As simplistic as this sounds, each individual must possess a carefully considered plan of action. This plan cannot be limited to "seeing patients." Each individual must demonstrate a needed and novel contribution. This contribution can be the possession of a skill that is not currently present in the global health setting with intent to teach that skill over time or the willingness to undertake a project for which there are not sufficient local personnel currently.

Partnership

Global health work occurs in teams. Each individual must demonstrate the existence of the team in which s/he will work. This team will likely include both overseas healthcare systems and their professionals and other US-based global health professionals. Where appropriate, these teams should maintain a "two-way" system of benefit wherein not only the US-based global health professionals but also the overseas professionals stand to gain from the collaboration, ideally equally. By identifying a team, US-based health professionals will be plugged into existing healthcare infrastructure and hopefully avoid redundant care. Some have proposed that ethical review must occur at the level of the local community,4 and this qualification attempts to address that critical critique.

Language Fluency/Ability to Communicate

The visiting US-based health care professional cannot be so linguistically limited as to be completely dependent on others. Language competency or the use of compensated translators should be the stated aims, knowing that overseas settings can often be so busy that the extra time good translation requires makes language competency the first among equals. Some hospital systems already make use of testing to establish if health care personnel have enough competency in a language to use it to communicate with patients and their families. This same testing system could be applied to the IRB process and perhaps run concurrently with the face-to-face interview.

Cultural Competence/Historical Background

This is perhaps the characteristic which is most difficult to readily measure, but each individual should have a sense for the social norms, history, geography, political realities and quirks of a place.

Funding

Individuals should be able to demonstrate access to funding for all proposed work in global health settings.

Track Record

As noted previously, each individual should be graded against a level of commitment appropriate for their level of training and previous global health work. Individuals with lengthy histories of collaborative publications and systems improvement can be given more flexibility in proposed work, while those with a history of one-off trips should be closely scrutinized.

Redundancy

The IRB can serve as a check of two or more individuals about to undertake redundant work or serve to connect those where collaborations seem possible.

In a review of the requirements for visiting international students posted on various US medical school websites, most require a clear plan, documented language competency (often via formal testing), cultural competence and funding / tuition documented in advance prior to acceptance into any programs. If we recognize the importance of these criteria in our own facilities, we must also recognize their importance when our people travel to other care settings. Ultimately, the IRB must have the ability to say "No" to an applicant / small group whose project is either terminally misguided or unable to address the IRB's concerns much as US based institutions can say to overseas visitors.

IRBs as Global Health Screeners – An Idea, but Not a Perfect Idea

Individuals who have worked with US academic center IRBs in international arenas are very likely dubious of this suggestion. IRBs are notorious for making requests that are untenable if not impossible in many lower resource settings. IRBs can make requests of researchers based on assumptions about infrastructure or patient populations that work well in their home setting but which might be problematic in low resource settings. Examples may include the proper storage of biological samples at -60 degrees Celsius or the literacy of possible

study participants affecting how informed consents can or should be performed. For the researcher working with the IRB in the IRB's traditional role, these frustrating interactions can make one feel a large disconnect between one's US-based institution and one's global research setting.

These are fair concerns. As regards serious global health work and medical voluntourism, the IRBs will not adjudicate the overseas work unlike traditional research. The IRBs likely do not need to be particularly familiar with the overseas setting outside of monitoring language competency. The IRB does, however, need to be able to block or bless an individual's work based upon the above criteria. If an IRB is aware of a care provider who treats chronic diseases but who is not a partner with a team or healthcare system that can provide the long-term follow-up care chronic diseases demand, the IRB does not need to know the country or region of interest to know that this individual's work is in need of additional foresight.

Many will justifiably point out that much medical voluntourism is occurring in settings outside of academic institutions, such as religious groups or non-governmental organizations (NGOs). In the case of the latter, they often possess permanent staff (including locals) with a clear mission and focus that all individuals working with said NGO must follow. Many NGOs do laudable work; others have been linked to questionable practices. Nonetheless, a burgeoning industry related to short term overseas work grows constantly around many of them. Such work cannot be adjudicated similarly to the proposals in this piece, as neither religious groups nor NGO's tend to have an independent, intra-agency body capable of (near) bias-free self-critique. These groups cannot be the gatekeeper of global health work much as researchers are no longer allowed to be of research and global health professionals should no longer be allowed to be of medical voluntourism. This is why research done by NGOs in conjunction with US academic center based global health professionals must still be reviewed and approved by the IRB. While IRBs can address this research, the use of IRBs at US-based academic medical centers cannot stem the tide of short term overseas work and its related issues within the larger issue of voluntourism.

Finally, this idea would require the expansion of the IRBs themselves. Many IRBs are already heavily over-subscribed and this task would only add to their workload. This shortcoming is undeniable. More people would need to be hired. It may be that small, separate, global health focused "sub-IRBs" would need to be created within the larger superstructure, initially at institutions with larger global health presences and then at other facilities as needed. Different institutions would put these suggestions in place on a case-by-case basis as no one approach would serve all academic centers. Nonetheless, the speed at which global health and its associated voluntourism is expanding demands difficult but important interventions and the IRB's presence and skill set often a unique opportunity. The issue of voluntourism will only become harder to curb.

Conclusion

Widespread concern about medical voluntourism exists due to its creating of redundant and inappropriate care without proper short and long term follow up, while also molding the local health workforce to suit its own needs.[2,5-12,16], 17 A workable solution to addressing voluntourism has not been found in the form of a new bureaucracy or diploma/degree program, though these programs are laudable and important. The current status quo of individual-level monitoring is not working. This paper presented the case for US-based academic centers to place this control in the hands of pre-existing IRBs. Despite the shortcomings of this idea, there is a need for formal, comprehensive review of all global engagement at the level of the individual, much as IRBs themselves were created in a time when there was a new recognition of a need for formal ethical review of all research activities. IRBs are existing, geographically widespread ethical bodies that can consistently and independently address the ethics of global health professionals occurring at their respective institutions, while allowing for some local flexibility within a larger ethical framework.

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How Smartphone Technology is Changing Healthcare in Developing Countries

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It is widely recognized that technology can improve the health of populations in countries around the world. Smartphone technology is at the forefront of innovation in low, middle and high-income countries. Due to the falling price of the smartphone, and the United Nations (UN) commitment to make Internet access available in the least developed countries by 2020, soon smartphones will be available to all. This technology has already improved the doctor-patient interaction, reducing costs and improving care for patients. The benefits range from cheaper, quicker medical education to point-of-care ultrasound. This article explores the most recent developments, discusses future applications of smartphones and investigates how people's lives in developing countries are being altered by this technology.

Introduction

The importance of technology in healthcare is becoming increasingly evident. Resolution 60.29 of the World Health Assembly commented that Health Technologies are "indispensable for effective and efficient prevention, diagnosis, treatment and rehabilitation of diseases."[2] The smartphone can play a central role in making this resolution a reality and is becoming more accessible for millions around the world.

In 2014, the World Health Organization (WHO) launched its second Global Health Initiative, calling for affordable and practical technology for low- and middle-income countries.[3] The UN development goal 9c aims to deliver "universal and affordable access to the Internet in the least developed countries by 2020."[4] This may sound like an ambitious objective, but the plummeting price of the smartphone is making it a real possibility.

Nearly a billion smartphones were sold during 2013, with most shipping to emerging markets: 283 million in China, 125 million in India, 47 million in Brazil and 46 million in Indonesia.[5,6] Government schemes in Ghana and Malaysia have also enabled consumers to purchase smartphones. Ghana has a 20% decrease in tax for smartphones and Malaysia has developed a rebate scheme for low-income youths, enabling many to purchase smartphones.[32,33]

The uptake and usage of smartphones is unprecedented. More people are using smart phones and taking an active interest in personalized healthcare. Using this data and the opportunities smartphones present are crucial.

Improving Communication and Training for Healthcare Professionals

Smartphones encourage doctors to collaborate and enable quicker communication between health services. This apparent "health communication" is an emerging field and one of increasing importance to nearly every aspect of health and medicine as a profession.[7]

Rapid developments in cloud-based storage systems promote collaboration and sharing of files on mobile devices.[8] Healthcare professionals have instant access to images and test results whenever they require. It is important that these applications have had rigorous security checks as to uphold patients' right to confidentiality.

Social networking connects doctors, students and patients globally. It can be used to share knowledge, to provide feedback and to increase health awareness. However, the appropriateness of the communication platform and the type information the doctor is able to reveal needs to be considered to ensure the boundaries of doctor-patient interaction do not become blurred. The General Medical Council has released guidance related to this.[9] Doximity, a social network designed exclusively for doctors, has 400,000 registered physicians.[10] It aims to promote professional communication and networking, which allows doctors to collaborate on rare cases and share insights into the medical world.

The WHO estimates the world needs an additional 12.9 million skilled health professionals including midwives, nurses and doctors by 2035.[11] Learning conducted via electronic media (e-learning) can partially fulfill this shortfall. Universities, government health agencies, NGOs and private companies are investigating how best to embrace this technology. The University of Washington's Department of Global Health is leading the way for distance learning in low-resource settings. Their Dept. of Global Health E-Learning Program (eDGH), which began in Kenya and Haiti, now runs in 30 countries.[12] The program's flagship course "Clinical Management of human immunodeficiency virus (HIV)" reaches over 1000 healthcare students globally each year.

Being able to use tablets and smartphones in the training of doctors can help to train more healthcare professionals in low and middle-income countries. Greater numbers of doctors and nurses being trained means better care for patients around the world.

E-learning, cloud-based technologies and social networking facilitate the training of medical professionals and improve the communication between professionals. This may speed up administration and improve services for patients but does not involve patient participation or their interaction.

Cooperation to Improve Care

Smartphone technology is aiding patient management as well. iWander is an app which that monitors Alzheimer's patients through a small GPS tracking device.[13] iWander involves a discrete monitoring device located in a watch which can, upon evaluation, provide several different courses of action from directing the patient home to performing a group call to emergency services and the caregiver.

In an interview with the BBC, Sir Bruce Keogh, Medical Director of the NHS, stated, "the hospital of the future is in the home."[14] Integrating wireless sensors into everyday objects has enabled medical data to be generated and stored on our smartphones. Soon, wristwatches that continuously and passively monitor blood pressure

and vital signs will become the norm.[15] Other wearable monitors currently under development include contact lenses that check glucose levels or eye pressure, necklaces for 24-hour ECG monitoring and headbands that have integrated electroencephalography sensors.[31,30,27]

These devices allow patients greater control over the investigations into their health they receive. The smartphone allows patients to track their health and gives greater control in the doctor-patient relationship. It is a manifestation of the shift of patient empowerment and shared decision-making.

Reducing Healthcare Costs

Smartphone technology is inclusive. Although it may seem much of this technology is aimed at higher income countries, developing countries are keeping up with incredible innovation and creativity.

In India, 60 million people have type 2 diabetes, 36 million have hepatitis B and 2.6 million have HIV.[16,17] Investigating, monitoring and managing large numbers of patients is incredibly complex. To tackle this problem, an Indian public health doctor has created the Swasthya Slate or "Health Tablet." Funded by the Public Health Foundation of India, this technology is viewed as the future of medical investigations in primary care and rural areas of India.[18] It is a portable diagnostic device that can record blood glucose, hepatitis B status, HIV status and 30 other diagnostic tests. This means doctors can diagnose, monitor and treat patients' chronic illnesses at the point of care.

Smartphone technology has aimed to decrease the price of everyday medical devices. Kenek O2 is a pulse oximeter that connects to smartphones.[19] The combined cost of a smartphone and pulse oximeter is $65, which is 1/100th of the cost of a normal oximeter.[20] Even a smartphone compatible ultrasound machine has been developed.[26] This has revolutionized point of care ultrasound (POCUS). Using this device, doctors can place central lines, guide injections, diagnose emergencies quicker and scan pregnant women in remote areas. POCUS is an excellent example of the developing world leading technological innovation. Doctors in developing countries such as Ethiopia, Indonesia, Sierra Leone and Kosovo quickly recognized the importance of POCUS.[21] They applied this safe, revolutionary technology in remote settings, resource scarce environments and emergency situations.

The power and intuitive nature of smartphones encourages innovation. World-leading technology is available at a fraction of the cost, and all are making the most of the opportunity.

Examples Of Current Uses In Developing Countries

In the Tanzanian village of Shirati, Dr. Buire Changi, chief medical officer, is in charge of a 200-bed hospital.[1] He frequently diagnoses skin conditions such as Kaposi's sarcoma and candidiasis in HIV positive patients. Despite his experience, Dr. Changi may need a second physician to confirm his findings. His patients need to be triaged and some referred to a larger hospital. The decision to seek a second opinion is crucial. If Dr. Changi chooses to refer the patient, it is an expensive five-hour bus journey to the Mwanza regional hospital.

He uses First Derm, a mobile app that enables him to use a smartphone-connected dermatoscope to take photographs of his patient's skin lesions.[1] These photos are then reviewed by a consultant in Dar es Salaam and the patients are triaged. Though the patients may still have an uncomfortable five-hour journey to Mwanza, they are referred with confidence that the journey is worth the discomfort.

In the future, smartphone technology could prove vital in dealing with difficult scenarios that may emerge in the developing world. Consider the implication of such technology in a situation similar to the outbreak of Ebola across West Africa in 2013. A future government may possess the technology to track people's mobile phones to gather information about movement patterns, isolating high-risk areas enabling the government to channel resources accordingly. Point-of-care testing can detect the Ebola virus in a single drop of blood. Virus control could be rapidly restored, and an epidemic is prevented.

Smartphone technology is already widely used in healthcare and has growing recognition across all medical fields. It promotes global interaction, improves care and reduces healthcare costs. If encouraged alongside a wariness of potential dangers, smartphone technology will continue to revolutionize global health and change the world.

Complications

At last count, there are over 229 apps in dermatology alone.[22] Many apps, such as Dr. Changi's in Tanzania, serve as educational resources and communication devices. However, the pharmaceutical company Bayer has also invested in a free app with similar properties.[23] The app is aimed at children but constantly informs the user about Bayer's topical steroid Desonate. If one of the purposes of an app is to generate profit, can the information the app provided be deemed impartial and valid? A systematic review of 103 self-management apps for asthma concluded that none provided combined reliable, comprehensive information about the condition with supportive tools for self-management and some were even considered to be unsafe.[34] Embracing technology but also remaining cautious and skeptical about the information it presents is key for all users and healthcare professionals alike.

Over 100,000 healthcare apps are already available.[25] These apps are available to anybody with a credit card and a smartphone. The rapid emergence of these apps has led to further concerns surrounding some of the ethical pillars of healthcare. A survey of 144 public and private healthcare leaders revealed that the biggest concerns for healthcare included the fear that "people may misinterpret their own data and make poor decisions" and unease regarding "data privacy risks."[24] These concerns may reflect the failure of privacy and security laws surrounding the collection and management of user's data by mobile-health apps to adapt.[35] Some users of these apps maybe in danger of assuming the health information they choose to share will be handled with the same ethical rigor that a healthcare professional would. Governing bodies and doctors must be vigilant and seek to educate users about the possible dangers.

"While the gold standard of care (e.g. catheterization for acute ST elevation MI or pacemaker placement for complete heart block) may not be available in resource-poor settings, Electrocardiograms (ECGs) may still assist in making correct diagnoses."

"A systematic review of 103 self-management apps for asthma concluded that none provided combined reliable, comprehensive information about the condition with supportive tools for self-management and some were even considered to be unsafe."

Attempts have been made to regulate health-related smartphone technology. In the U.S., medical apps that present a real risk to patients if they do not work as intended need to be approved by the Food and Drug Administration.[36] However, there is controversy surrounding which apps need to go through the accreditation process before they are distributed to the public.[37] Similarly, in the EU, the CE certification or *Conformité Européenne* marks products that comply with relevant EU legislation.[38] In the UK, the NHS went a step further and launched a health app pilot site in 2013 to review and recommend apps against a defined set of criteria.[39] However, an independent assessment of 79 apps certified as clinically safe and trustworthy by the NHS Health Apps Library revealed that 89% of the apps transmitted information to online services and concluded there were "systematic gaps in compliance with data protection principles."[40] The Health Apps library is currently being upgraded to improve its vetting process, highlighting the need for a consistent and reliable accreditation system that alerts consumer to possible deficiencies and dangers within the apps. Until a system is in place that requires developers to rectify these vulnerabilities before the technology can be released, education will continue to be the first and foremost line of defense.

Conclusion

This article examines a fraction of possibilities that smartphone technologies present to change healthcare around the world. The smartphone's ever expanding sphere of influence could enable it to become the future of global health.

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