THE USE AND SAFETY OF ANTIRETROVIRAL MEDICINES - LESSONS FROM GHANA

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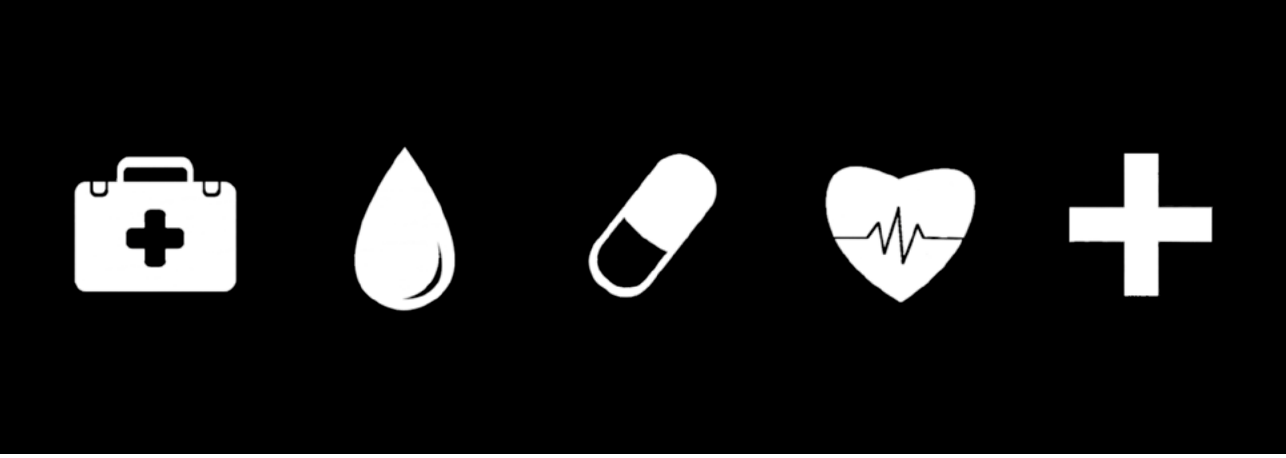

Chapter 1

INTRODUCTION

EPIDEMIOLOGY OF HIV/AIDS IN GHANA

Acquired Immunodeficiency syndrome (AIDS) is a combination of symptoms, signs and infections resulting in chronic damage to the human immune system caused by the human immunodeficiency virus (HIV) [1]. HIV/AIDS is presently classified as a pandemic event [2] since an estimated 33.2 million people live with the disease. To date over 4 million worldwide have died from HIV/AIDS related outcomes including over 600,000 children [3]. More than three-quarters of these deaths occurred in sub-Saharan Africa, destroying human capital while retarding economic growth [2,3]. Ghana is classified as having a generalised HIV epidemic with HIV prevalence hovering around 2% in the last decade [4]. By the end of 2015, 274,562 persons were living with HIV with women constituting 60%. The country recorded total annual AIDS deaths of 10,958 in the same year. Cumulatively from 1986 when the first case of HIV/AIDS was discovered, over 200,000 deaths have been documented [4,5].

However, recent reports from UNAIDS indicate the scales are tipping and for the first time more than half of all people living with HIV/AIDS (PLHIV) worldwide almost 53%, now have access to HIV treatment [3]. Consequently, AIDS related deaths have almost halved since 2005 from 1.9 million in 2005 to 1 million in 2016 [3]. The World Health Organisation (WHO) reports that eastern and southern Africa, the regions most affected by HIV and which account for more than half of all people living with HIV, is showing the most progress. Since 2010, AIDS-related deaths have declined by 42%, with new infections dropping to a low of 29%, including a 56% drop in new infections among children over the same period [2,3]. In Ghana, the National HIV Prevalence and AIDS Estimates Reports for 2011 to 2016 show the national HIV response is making good progress. The number of new infections reduced from 12,077 in 2011 to 7,991 in 2012 reflecting a 34% drop in a single year [5]. These remarkable achievements are mostly due to the use of antiretroviral drugs. In Ghana, 89,113 people were on antiretroviral therapy (ART) by the end of 2015 [6]. In 2016, globally 19.5 million out of the 36.7 million PLHIV had access to treatment. It is projected that by 2020, 30 million people could be on ART [5].

The WHO further estimates that 3 million percutaneous exposures occur annually among 35 million healthcare workers (HCW) worldwide, representing 12% of the working population [7]. While 90% of these occupational exposures occur in the developing world due to inappropriate universal protective measures, only a fraction of about 10% is reported globally, much against roughly 90% of reported incidents from the United States and Europe [7,8]. The Korle Bu Teaching Hospital (KBTH) in Accra, Ghana alone documented 500 of such incidents from 2003 to 2016 [9].

ART SERVICE IN GHANA

Antiretroviral therapy has been available in Ghana since 2003 [8,10]. Guidelines from the National AIDS/STI Control Program (NACP) indicate the use of ART in Ghana includes the provision of ART-service to PLHIV in HIV-clinics and the provision of post-exposure prophylaxis (PEP) to healthcare workers and sexually exposed victims of abuse/assault

[8,10]. Post exposure prevention of HIV infection following occupational exposure to HIV for health workers and victims of sexual assault has been used in Ghana since the early 1990s [10]. The provision of ART in HIV-clinics of the healthcare system started at two pilot sites in the eastern region of Ghana but has grown significantly to 195 treatment sites by 2015 [10]. The cumulative number of people with HIV infection initiated on antiretroviral therapy (ART) by the end of 2015 was 119,600 with the KBTH providing service to a sizeable amount of PLHIV at close to 25,000 [8,10]. The KBTH is the premier tertiary care facility in Ghana and presently manages the largest cohort of PLHIV in the country. HIV clinical care services in Ghana includes HIV testing, prevention of mother to child transmission, provision of ART, treatment of opportunistic infections, management of sexually transmitted infections and finally post-exposure prophylaxis for health professionals and rape survivors. These services are offered at all levels of the health delivery system by specially trained health professionals using standardized guidelines and manuals to provide high quality of care. ART is a lifelong commitment and distinctive strategies are necessary to ensure its effectiveness, low toxicity and prevent the development of drug resistance.

The initiation of ART in the KBTH was supported by Family Health International (FHI), an international non-governmental healthcare organisation, who provided a database which was used in capturing data on all patients registered by the HIV-clinic. The provision of ART services has contributed significantly to the reduction of HIV-related morbidity and mortality in Ghana over time [8]. Data from the NACP indicate that HIV prevalence in antenatal care clients was 3.6% in 2003 and has declined to 1.8% in 2015 [11]. This essentially shows a 50% decline in prevalence over the period, indicating the usefulness of ART in impacting greatly on the many lives, both in terms of reducing the number of being people infected with the virus as well as managing those infected and affected by HIV by improving their quality of life [11].

Over the period of 14 years of providing ART services, Ghana has transited from the initial guidelines based on the WHO recommendations which required that patients are initiated on ART at WHO clinical stage 3 & 4 and/or CD4 count of <500cells/mm [8,10] to the latest November 2015 WHO global approach of "Treat All" recommendations [10,11]. In addition, the country has also adopted the global UNAIDS 90/90/90 aspiration target [10,11] which aims at sustaining the positive impact of ART on the lives of PLHIV and possibly ending the AIDS epidemic by 2030. In order to achieve this remarkable feat, Ghana's national strategic plan (2016-2020) is to test approximately 13 million Ghanaians by 2020 and to increase ART coverage from the current 35% to 90%, by treating 229,920 people with ART [12].

Table 1 presents the combinations of ARVs recommended as preferred regimen in Ghana as according to current guidelines [5,13]. Additionally, fixed dose combinations of these ARVs are preferred to single entity preparations as they improve adherence due to reduced pill load [10]. A second line regimen is used when there is evidence of treatment failure with the first line regimen. A third line therapy is recommended for PLHIV who fail the second line treatment. Here drug resistant testing is recommended [10,13]. Unfortunately, third line ARVs are still not available in the program owing mostly to cost constraints.

Table 1. ART recommended regimen in Ghana as according to current guidelines

First line	Second line	Third line
TDF + 3TC/FTC + EFV TDF +3TC/FTC + NVP	TDF + 3TC/FTC + LPV/RI TDF + 3TC/FTC + ATV/RI	DRV/RI+DTG/RTG+ TDF/ZDV +3TC/FTC
OR	**OR**	**OR**
ZDV + 3TC/FTC + EFV ZDV +3TC/FTC +NVP	ZDV + 3TC/FTC + LPV/RI ZDV + 3TC/FTC + ATV/RI	DRV/RI+TDF/ZDV +EFV/NVP

3TC=Lamivudine; ATV=Atazanavir; DRV=Darunavir; DTG=Dolutegravir; EFV=Efavirenz; FTC=Emtricitabine; LPV=Lopinavir; NVP=Nevirapine; RI=Ritonavir; RTG=Raltegravir; TDF=Tenofovir; ZDV=Zidovudine

The provision of ART service as PEP to exposed healthcare workers to a potential HIV source patient are assessed by healthcare professionals including pharmacists for eligibility for PEP services. Mandatory HIV testing is required of the exposed healthcare worker to confirm HIV negative status before PEP is administered. PEP is recommended to be initiated preferably within 1-2 hours post-exposure and not more than 72 hours after exposure [14]. Baseline laboratory tests required include full blood count, liver and renal function and hepatitis B surface antigen. A prescription of PEP for the exposed healthcare worker is approved following a counselling session on the risk and benefits of PEP. ARV regimens for eligible healthcare workers include dual therapy of zidovudine/lamivudine or tenofovir/lamivudine or triple therapy with zidovudine, lamivudine and lopinavir/ritonavir or tenofovir, lamivudine and lopinavir/ritonavir, respectively, depending on whether the risk assessment indicated a low risk (dual therapy) or a high risk (triple therapy) [14,15]. Possible adverse effects of the antiretroviral drugs prescribed are discussed and the importance of completing the 28 days of PEP emphasized. The counselling sessions ensure that exposed healthcare workers who receive PEP report all adverse events during and after administration of the ARVs. Cohort event monitoring of clients via mobile phone calls are done to capture patients' self-reports on adverse events (AEs) [15]. A follow up review appointment to repeat the HIV test 3 months after the HIV exposure is done to determine HIV status and to monitor drug toxicity. The provision of HIV post exposure prophylaxis has presently been extended to other non-occupational exposures, including unprotected sexual exposure, injecting drug use and exposure due to sexual assault [15].

SAFETY MONITORING OF ANTIRETROVIRAL MEDICINES

New symptoms and signs could present after initiation of ART. These may include those associated with disease progression, adverse reactions to antiretroviral drugs and opportunistic infections could present as a consequence of immune reconstitution [10]. Much as ART has proven over time to be beneficial and lifesaving, antiretroviral agents are responsible for a broad range of adverse effects from low grade self-limiting to life threatening side effects [10]. Adverse effects to ART can lead to treatment cessation by PLHIV

or poor adherence resulting in poor treatment outcomes [14,16]. Differentiating between complications of the HIV disease and ART toxicity can be very difficult [10]. Clinicians must follow guidelines to ensure that ART is not stopped or switched unnecessarily; as a result of presenting complaints which may be disease related rather than ART related. The use of ART in any country therefore requires comprehensive monitoring of efficacy as well as toxicity.

Adverse events are a common complication of antiretroviral therapy. The incidence of adverse reactions is high at the onset of treatment but tends to decrease in later stages [10]. Long-term reactions such as lipodystrophy, paraesthesia, neuromotor disorders and increased risk of cardiovascular morbidities may occur. The most common adverse effects associated with discontinuation of ART are gastrointestinal related [16]. These include nausea, vomiting, diarrhoea and anorexia. These events can be non-specific and therefore difficult to distinguish as symptoms of the disease or adverse effects of the treatment. Common drug toxicities (inability of patient to tolerate side effects of ARV) encountered include haematological toxicity, mitochondrial dysfunction, renal toxicity, other metabolic abnormalities, allergic reactions, hepatic toxicity and muscular toxicity [10,16,17]. These toxicities are graded as 1= mild, 2 =moderate, 3= severe, and 4=severe life-threatening [10]. Specific adverse reactions are associated with various classes of ARVs. The NRTIs are associated with peripheral neuropathy, anaemia, lactic acidosis, hypersensitivity reactions and nephrotoxicity [16-18]. The NNRTIs are associated with rash, hepatotoxicity, and central nervous system effects like vivid dreams/hallucinations [16-18]. The protease inhibitors, used mostly for HIV 2 and PLHIV who fail the first line regimen, are also associated with risks of hyperlipidaemia, insulin resistance, fat redistribution and lipoatrophy [17,18].

Several studies have reported incidence rates as high as 54% in some instances [18-20]. The tolerability of some ART regimens pose challenges and concerns for patient care, and lately one of the nucleoside reverse transcriptase inhibitors, stavudine (D4T), was removed from our guidelines and replaced with tenofovir because the WHO considered its cumulative toxicity as unacceptable [10]. Non–adherence to treatment has been linked to the occurrence of adverse events in HIV patients, thereby influencing treatment outcomes negatively [18-20].

Adverse effects of ARVs should be explained to clients and where necessary appropriate measures taken. Guiding principles available to manage ARV associated adverse events support clinicians to take prudent decision on management before deciding on possible regimen switches, since available options of ARVs are limited in our resource challenged circumstances [10]. Regular laboratory monitoring is done after ART initiation to identify side effects, toxicities, viral suppression and drug resistance in individual patients. Therapy may be interrupted or discontinued by the clinician in discussion with patient and pharmacist in instances of intolerable side effects, severe drug interactions or poor adherence. The clinician may also consider ART regimen modification in instances of treatment failure in consultation with other HCWs in a multidisciplinary management team [10].

The high prevalence of adverse drug events among PLHIV has been identified as a major reason for patients defaulting [20,21]. Treatment failure as a result of poor compliance and

development of resistance to ART could be due to any of these reasons; poor prescribing practices, poor adherence, insufficient ART levels, insufficient ARV potency and unreliable drug availability [10]. The high prevalence of adverse events and the lack of clarity between manifestation of HIV/AIDS and presenting adverse reactions to ART influences clinicians to switch regimens through substitution of drugs from similar groups (NRTI or NNRTI) or through therapy switches from first line to second or third line regimens [21-23]. Various studies from Ethiopia [24] and India [25] reported the effects of recorded adverse events on ART modifications. The need for regimen switches becomes more pressing when long-term events such as lipodystrophy, renal impairment or intolerance present [24,26,27]. The issue of the relationship between occurrence of adverse drug events and ART switches deserves further study across several countries in order to prevent waste of resources as well as limit the development of resistance strains arising out of mutations.

The use of tenofovir based regimen as the preferred first line ART is also an issue of contention, given the known risk of possible renal impairment as a long term toxicity profile of tenofovir [28-30]. Various studies published findings against and in support of its use provided monitoring of renal function is undertaken regularly [28,30]. With the new policy of "Treat All" by the WHO more people living with HIV will be diagnosed and initiated on ART and more cases of possible renal impairment could be reported if prudent measures are not in place to monitor renal toxicity, especially in economically challenged settings. Active pharmacovigilance is required in all cases of tenofovir based regimens.

Patients initiated on ARVs remain on them for life. The need therefore to ensure adequate knowledge of the side effects and how to manage them and the need for maximum adherence to ensure positive outcomes is important. PLHIV are expected to go through several sessions of adherence counselling before initiation of ART. These sessions provide fair knowledge of the usefulness of ART in the management of HIV, and adverse reactions of ART and what to do in the event of adverse events. Several studies point to the fact that patients underrate the risks of their medications and lack of adequate knowledge increases the risk of AEs [30]. Other studies revealed that education and effective counselling results in positive attitudes of PLHIV towards compliance to ART and overcoming the AEs encountered [30,31].

Several studies from various countries showed that when ARVs were used for 28 days in PEP clients, a higher frequency of adverse events was reported compared with HIV positive patients taking similar medications [32,33]. This frequency is higher among PEP patients receiving triple therapy as against dual therapy [33-35]. The need to describe the outcomes of a PEP program and the adverse and adherence to ARVs in use in our setting is therefore important to inform policy and further manage future occupational hazards better. Published reports on the outcomes, adverse reactions and adherence of PEP programs are only available in a few countries in Africa, namely Nigeria [36], La Cote d'Ivoire [37] and Kenya [38]. The intolerance to adverse events was cited as the sole reason for truncating PEP, thereby indicating the need for adequate, appropriate and effective counselling, education, active follow-up (possibly through mobile/phone contact) and management of adverse events [39].

Available evidence supports the efficacy of ARVs as pre-exposure prophylaxis (PrEP) in reducing the incidence of HIV infections among high-risk individuals [40,41]. Several challenges confront the use of PrEP, amongst which safety screening, toxicity arising from continuous use, adverse drug reactions, poor adherence and possible abuse stands tall [40,42]. Although PrEP is an approved intervention to reduce HIV transmission and appears to have safe benefit-risk profile in clinical trials, considering the listed potential toxicities, a recommendation for real world safety surveillance is critical in the post- marketing phase of its use [44].

PHARMACOVIGILANCE IN GHANA

The WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse reactions to medicines or any other medicine-related problems [17,43,44]. When pharmacovigilance is made an essential part of patient care, the risks and risk factors associated with use of medicines can be identified early and this prevents or minimizes harm related to adverse drug reactions (ADRs). It is also reported that effective pharmacovigilance practice generates evidence to inspire public confidence and trust in any health care system [17,44,45]. Post-marketing surveillance (PMS) is important in quantifying previously known ADRs, capturing unrecognized adverse drug events and evaluating the effectiveness of medicines in use in bigger populations in order to decrease mortality and morbidity associated with adverse reactions. The WHO therefore recommends that pharmacovigilance should be part of every public health program that uses medicines in order to optimize the use of insufficient health resources and prevent potential tragedies [43,44].

An executive summary of findings by Nwokike and Eghan in 2010 [46], titled Pharmacovigilance in Ghana: A Systems Analysis on behalf of Management Sciences for Health, indicated that the Ghana National Drug Policy recognizes the need for pharmacovigilance and medicine information services and considers post-marketing surveillance and pharmacovigilance important aspects of medicines registration and selection in Ghana. The country, however, does not possess the legal provisions to enforce pharmacovigilance activities. Additionally, their recommendations have resulted in legal processes leading to the processing of legal support with a post marketing surveillance directorate being set up within the Ministry of Health [46].

Ghana became a member of the WHO program of international drug safety monitoring in 2004 [45], but has contributed little to the UMC database. In 2015, the Food and Drugs Agency reported that within a year, the National Pharmacovigilance Centre received an average of 12 ADR reports per 1,000,000 Ghanaians and these reports were presented mostly by health care providers. This falls far below the WHO recommendation of at least 200 to 250 reports per million populations per year [45]. In Africa in general, the pharmacovigilance systems in place are mostly new and still developing [17,44]. Ampadu et al., reported that 35 of the 55 African countries are members of the WHO Program for International Drug Monitoring as

at 2015, and these 35 countries contributed less than 1% of the global reports in the WHO database of spontaneous pharmacovigilance reports, Vigibase® [47]. The analyses again showed that almost one-third of all reports from Africa were on HIV and AIDS treatment with about 1.9% on anti-tuberculosis medicines use [47]. A picture of poor and gross underreporting of adverse drug events is clearly painted, with the resultant effect of greater possibility that safety issues regarding medicines use, and in this case use of ARVs, could go undetected and negatively affect the country's attempt to provide quality healthcare.

AIMS AND OBJECTIVES OF THE THESIS

The theme of this thesis looks at two components of the HIV clinical services, namely provision of post- and pre-exposure prophylaxis and the ART services for PLHIV. The aim was first to investigate the use and safety of ARVs in post exposure prophylaxis for healthcare workers exposed to body fluids of PLHIV and safety of pre-exposure prophylaxis, and secondly to investigate the pharmacovigilance of ARVs in PLHIV. The objectives were to document outcomes and adverse events of PEP in Ghana, discuss the safety concerns of PrEP as observed in clinical trials, document adverse events associated with ART, its effects on treatment modifications and evaluate the knowledge and attitudes of PLHIVs to ARVs in Ghana.

OUTLINE OF THESIS

This thesis is organized into four main chapters;

Chapter 1 provides an overarching introduction of the research topic, the aim and objectives of the research activities undertaken.

Chapter 2 explores occupational exposures to HIV infection by healthcare workers, the use of anti-retrovirals as post-exposure prophylaxis and the associated adverse events, and safety of pre-exposure prophylaxis. **Chapter 2.1** presents the outcomes of a PEP program in the Korle Bu Teaching Hospital in a retrospective cohort study that looked at the utilization of a risk assessment system to manage health workers and students exposed to HIV infected body fluids and the study outcomes. **Chapter 2.2** reports adverse events and adherence to PEP by healthcare workers and students by deploying an active pharmacovigilance tool of cohort event monitoring (CEM) to follow up on healthcare workers and students who presented for PEP services following occupational exposure to HIV infected body fluids of PLHIV. **Chapter 2.3** reviews clinical trials on the safety of ARVs use as PrEP in HIV negative clients at risk of HIV infection due to risky lifestyle or in sero-discordant relationships.

Chapter 3 investigates a number of important aspects in pharmacovigilance of antiretroviral medicines used in PLHIVs. **Chapter 3.1** investigates the association between the occurrence of adverse events and the modification of first line anti-retroviral therapy in Ghanaian PLHIV. It uses an unmatched case control study design to compare cases (those with a modified regimen) against controls (same index start date but regimen not modified). The study also documents adverse events reported by patients or observed by clinicians.

Chapter 3.2 investigates longitudinally the occurrence of renal toxicity of a tenofovir based regimen in PLHIV whose baseline creatinine clearance (CrCl) is in the normal range but may develop renal injury over the six-year study period. **Chapter 3.3** presents findings of the knowledge, attitudes and practices of PLHIV concerning AEs experienced on ART. A cross sectional study using a likert scale is administered to PLHIV to assess knowledge of AEs and attitudes to AEs. Factor analysis is used to reduce dimensions of attitudes observed to relevant latent constructs underlying different types of behaviors.

Chapter 4 is the concluding chapter of the thesis. It presents the overarching discussion of the findings of the various studies undertaken, the benefits of ARVs as PEP and the risks of AEs identified among healthcare workers and students. Recommendations are made to improve on PEP. It also looks at the toxicity associated with chronic management, the limitations in monitoring and reporting AEs, the knowledge and attitudes of PLHIV, and the modifications of treatment regimens in resource limited settings like Ghana. Policy implications and recommendations are made to inform the Ghana AIDS Commission, the Ministry of Health and the National AIDS/STI Control Program. Included also are prospects for future research to determine real-world safety issues overlooked or cited as limitations in our studies.

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Chapter 2

POST AND PRE-EXPOSURE PROPHYLAXIS FOR HIV INFECTION

Chapter 2.1

OUTCOMES OF A POST EXPOSURE PROPHYLAXIS PROGRAM AT THE KORLE-BU TEACHING HOSPITAL IN GHANA: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

The risk for occupational exposure to HIV is a serious public health problem that is well characterized in the developed world, but less so in the developing countries such as Ghana. This study was undertaken to examine the characteristics of occupational exposure to HIV and the utilization of a risk assessment system (RAS)–based postexposure prophylaxis (PEP) among health care workers (HCWs) and health care students (HCSs) in the Korle-Bu Teaching Hospital (KBTH). During the study period (January 2005–December 2010), a total of 260 and 35 exposures were reported by HCWs and HCSs, respectively. Ward attendants reported the highest incidence rate of 6.46 of 100 person-years (P-Y). The incidence of high-risk exposures was 0.33 of 100 P-Y (n = 65); 60.0% occurred during a procedure of disposing of a needle and 24.6% during a cannula insertion. A total of 289 of the 295 individuals were administered PEP, of which 181 (62.6%) completed the 6-month follow-up testing schedule and none sero-converted. This shows that with a good RAS in place, it is possible to deploy an effective PEP program in a typical African teaching hospital like the KBTH in Accra, Ghana.

INTRODUCTION

Health care workers (HCWs) represent the human resource capacity of any health care delivery system in any country. However, in their activities and duties, they are continuously exposed to all types of risks including exposure to blood and other body fluids, which may pose a risk of infection by the HIV and other blood pathogens [1,2]. The World Health Organization (WHO) estimates that 3 million percutaneous exposures occur annually among 35 million HCWs worldwide, which represents 12% of the working population [3]. It is worth noting that while 90% of the occupational exposures occur in the developing world, 90% of the reports of occupational infections occur in the United States and Europe [4]. There is clearly underreporting of occupational exposures in developing countries, which could be attributed to several factors including ignorance about occupational exposures and their management, lack of avenues for easy reporting, lack of protection for workers, and absence of postexposure prophylaxis (PEP) programs [4].

Postexposure prophylaxis, which involves the administration of antiretroviral (ARV) drugs, has been estimated to reduce HIV infection by about 81% [5] but this is most effective within 1 to 2 hours of exposure and not more than 72 hours after exposure [1]. Postexposure prophylaxis is hence a very important requirement in health care settings where workers are often exposed to body fluids. While published data exist on the outcomes of PEP programs in a few countries in the West-Africa sub-region including Nigeria [6-8] and La Cote d'Ivoire [9], no publication is available on Ghana, although PEP services in Ghana started in 2004.

In December 2003, Ghana, with a population of approximately 25 million and an estimated HIV adult sero-prevalence of 1.7% to 2.2% (425 000 patients living with HIV) [10] started providing antiretroviral treatment (ART) to persons living with HIV/AIDS (PLWHA) [11]. Although data specific to HIV prevalence among hospitalized patients are limited, it is estimated to be higher than that of the general population. Ghana, being a resource-constrained country, is faced with numerous economic challenges and thus the provision of requisite universal precautions necessary to protect HCWs comprehensively remains a goal being pursued. As part of a scaling up exercise to extend ART to PLWHA in all parts of the country by the National AIDS/STI Control Program (NACP) and in conformity with the "3 by 5" policy of the WHO, guidelines on the use of PEP were developed to ensure the provision of PEP in all sites that offer clinical care to patients living with HIV [11]. The present study was therefore under-taken to provide information on the provision of PEP in Ghana using information from 1 of the 4 pilot sites for ART delivery in Ghana—the Korle Bu Teaching Hospital (KBTH), an urban government premier teaching hospital in Accra. Data collected between January 2005 and December 2010 were analyzed to give the Ghana example of a PEP service in a resource-constrained setting and the effectives of an implemented risk assessment system (RAS) in reducing the rate of HIV sero-conversion.

METHODS

2.1

The study was a retrospective cohort study. The cohort was assembled from historical records on HCWs and health care students (HCSs) who reported exposure and requested for PEP at the Pharmacy Department of the KBTH between the period of January 2005 and December 2010. The study involved giving each reported exposed HCW/HCS a unique study ID based on the hospital's staff registry or student's identification list, which ensures that any multiple reported exposure is detected and captured appropriately. The study protocol was approved by the Ethical and Protocol Review Committee of the University of Ghana Medical School [MS-Et/M.6-P.5.3/2009-10].

Setting

The Korle Bu Teaching Hospital started providing care to HIV-infected patients in December 2003. Software developed by Family Health International was used to capture data on patients and to monitor the use of the ARV drugs. Guidelines on PEP service was developed by the institution based on the recommendations of the US Centers for Disease Control and Prevention (CDC) [1]. A team of health care professionals made up of medical and pharmacy personnel were charged with the responsibility of providing the PEP service and capturing data on HCWs/HCSs who report for PEP. Posters advertising the service and listing the mobile phone numbers of physicians and pharmacists in the PEP team were posted at all clinical departments of the hospital. Approximately 1930 HCWs and 1400 HCSs per year provide services at the hospital, and an initial sensitization exercise was done to ensure awareness among the staff. Subsequently all incoming students and interns were orientated on the PEP service.

Exposure Management

The procedure for managing PEP at the KBTH is as follows: any exposed HCW/HCS reports the incident to the immediate supervisor who directs the staff to a physician listed in the PEP team. The physician examines the exposure, determines the HIV status of the staff and the source patient, and then directs the exposed staff to a listed pharmacist who provides counselling and PEP medications, if considered necessary. Figure 1 shows a flowchart of the management procedures.

Risk Assessment System

In determining whether to administer PEP, a risk assessment of the exposure is carried out using both the 2001 CDC occupational exposure guidelines [1] and the local policy in place at the KBTH [11]. This system considers the risk versus benefit analysis for every individual presenting following an exposure, and the decision to initiate PEP is made on a case-to-case basis. Exposures classified as high risk were administered 28 days of expanded PEP regimen, moderate risk exposures were also administered 28 days of expanded PEP regimen, and low risks were administered 3 days of stat dose until the source patient's HIV status is

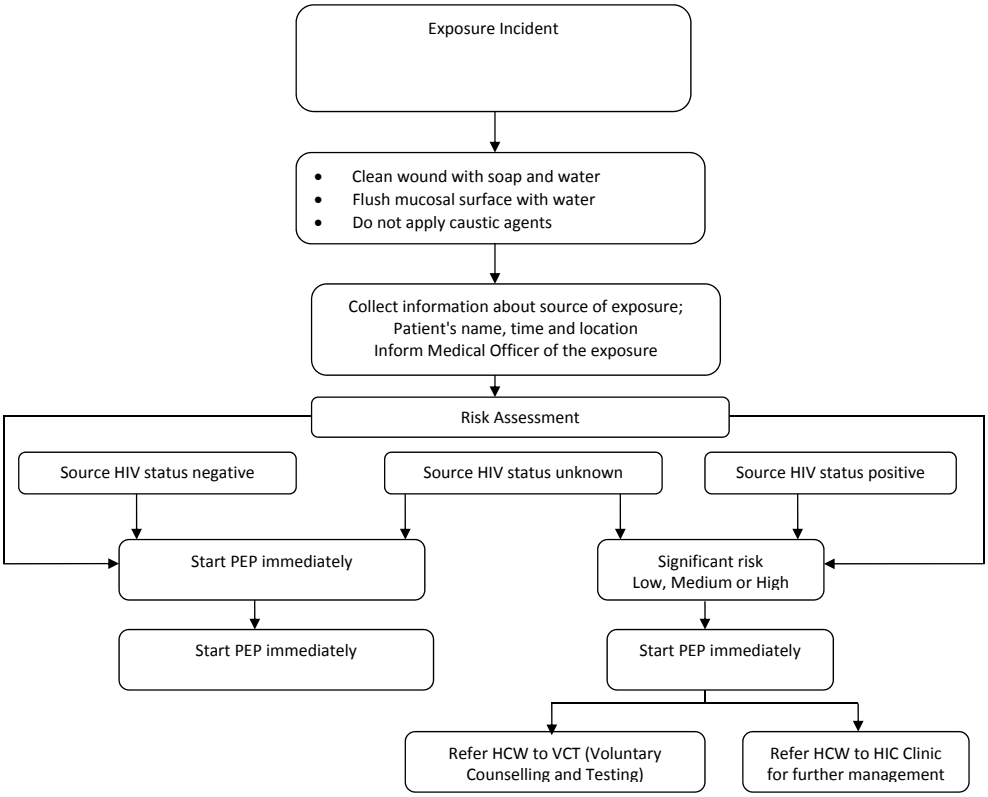

Figure 1. Occupational postexposure prophylaxis flowchart

determined. The stat dose given in all cases was a 3-day course of zidovudine (ZDV) and lamivudine (3TC) as dual therapy or ZDV and 3TC and lopinavir/ritonavir (LPV/r) as triple therapy. The same medications were continued up to 28 days as expanded PEP (in both dual and triple therapy as the case may be), based on the confirmation of the source patient's HIV status being positive or on one-to-one case decision by the risk assessment team in charge of using the RAS.

Data Collection

The data analyzed were collected from January 2005 to December 2010, a period of 72 months. A data collection instrument was developed in-house to capture the details of exposed HCW/HCS, the source of exposure, laboratory findings, and risk assessment, which is based on the details of the event, time of event, reporting time, and type of exposure. Additional information collected included the type of PEP medication regimen received by the exposed HCW/HCS in addition to the recording of adverse events (AEs) and the level of adherence to the treatment regimen over a total of 3 days/28 days. Data on HIV status as an outcome of PEP provision were also collected during follow-up testing schedules of 6

weeks, 3 months, and 6 months after PEP administration. During follow-up visits, data were collected on reported AEs and adherence to treatment regimen on exposed HCWs/HCSs but will be discussed in a subsequent article.

2.1

Statistical Analysis

All statistical analyses were performed using SPSS Version 19.0 (IBM, Armonk, New York). Incidence rates were determined for the various categories of HCWs and HCSs. Person time as 100 person-years (100 P-Y) was calculated using the assumption that each HCW and HCS was available all-year round over the study period. Risk of exposure to injury warranting PEP intervention was calculated for each category of HCW, with nurses as the reference profession. One-way analysis of variance was also performed to assess trends in proportions of exposures and behavioural types over the study period of January 2005 to December 2010.

RESULTS

Characteristics and Rates of HCWs/HCSs Reporting Exposures

During the study period, 260 HCWs and 35 HCSs reported a total of 295 occupational exposures without any multiple report (a total of 1930 HCWs and 1400 HCSs works in the KBTH yearly). The median age of exposed HCWs and HCSs was 28 years and 21.5 years, respectively. Of the exposed HCWs/HCSs, 175 (59.3%) were female (Table 1). Five departments, namely, child health, obstetrics and gynaecology, surgery, medicine, and surgical/medical emergency and trauma accounted for 71.5% of reported exposures (Table 1). Department of surgery recorded the highest reported number of exposures (53 HCWs, 18.0%) of which the majority (48 reports, 90.1%) were due to needle-stick injuries. In all, the 5 departments also recorded the highest number of needle-stick injuries (183 reports, 62.0%).

The greatest number of exposures was reported among nurses (116 reports, 39.3% of all reports) followed by physicians (95 reports, 32.2%). However, ward attendants reported the highest incidence rate of 6.46 of 100 P-Y (Table 2). Ward attendants were 4 times more likely to be exposed than nurses (relative risk [RR], 4.01, 95% confidence interval CI 2.90-5.55; $P < .001$). Health care students were the least likely to be exposed compared with nurses (RR, 0.26; 95% CI, 0.18-0.37; $P < .001$). A total of 80% of the exposed HCWs reported their exposure within 24 hours, while 82.9% of the HCSs also reported their exposures within 24 hours; the median time between exposure and reporting was 2.0 hours in both HCWs and HCSs. Follow-up telephone calls to all exposed HCWs/HCSs in the cohort administered PEP (289 individuals) during the 3 days/28 days treatment schedule showed a complete adherence to medication of 77.2% (n = 183), with 37 lost to follow-up.

Exposure and Exposure Source Description

Of the total 295 exposures, 271 (91.9%) were percutaneous and 24 (8.1%) were mucocutaneous (Table 1). A total of 277 (93.9%) exposures were due to handling/after a procedure with

Table 1. Characteristics of 295 HCWs/HCSs Reporting Occupational Exposures at KBTH in Accra, Ghana

Characteristics	Total N, %[a]	Exposure Risk		
		Low n, %[b]	Medium n, %	High n, %
Gender				
Male	**120 (40.7)**	65 (54.2)	29 (24.2)	26 (21.6)
Female	**175 (59.3)**	100 (57.1)	36 (20.6)	39 (22.3)
Median age (yrs), range; (n=285)	**28, 18-60**	28, 18-58	28, 19-60	30, 19-59
Profession				
Health care students	**35 (11.9)**	22 (62.9)	11 (31.4)	2 (5.7)
Laboratory staff	**18 (6.1)**	7 (38.9)	4 (22.2)	7 (38.9)
Nurses	**116 (39.3)**	71 (61.2)	17 (14.7)	28 (24.1)
Physicians	**95 (32.2)**	46 (48.4)	24 (25.3)	25 (26.3)
Ward attendants	**31 (10.5)**	19 (61.3)	9 (29.0)	3 (9.7)
Department				
Surgery	**53 (18.0)**	37 (69.8)	10 (18.9)	6 (11.3)
Medicine	**34 (11.5)**	13 (38.2)	8 (23.5)	13 (38.2)
Child Health	**47 (15.9)**	29 (61.7)	12 (25.5)	6 (12.8)
Obstetrics & Gynecology	**37 (12.5)**	22 (59.5)	7 (18.9)	8 (21.6)
SME &Trauma	**40 (13.6)**	26 (65.0)	9 (22.5)	5 (12.5)
Polyclinic	**33 (11.2)**	12 (36.4)	7 (21.2)	14 (42.4)
Central OPD	**20 (6.8)**	6 (30.0)	5 (25.0)	9 (45.0)
Others	**31 (10.5)**	20 (64.5)	7 (22.6)	4 (12.9)
Exposure Type				
Mucucutaneous	**24 (8.1)**	9 (37.5)	5 (20.8)	10 (41.7)
Percutaneous	**271 (91.9)**	156 (57.6)	60 (22.1)	55 (20.3)
Exposure Means				
Bloody bite	**1 (0.3)**	0 (0)	0 (0)	1 (100)
Bloody cut	**3 (1.0)**	1 (33.3)	1 (33.3)	1 (33.3)
Canula	**24 (8.1)**	4 (16.7)	4 (16.7)	16 (66.6)
Dental instrument	**1 (0.3)**	1 (100)	0 (0)	0 (0)
Knife cut	**1 (0.3)**	0 (0)	1 (100)	0 (0)
Needle stick	**246 (83.4)**	151 (61.4)	56 (22.8)	39 (15.8)
Pair of scissors	**1 (0.3)**	1 (100)	0 (0)	0 (0)
Piercing	**1 (0.3)**	1 (100)	0 (0)	0 (0)
Scalpel blade	**3 (1.0)**	0 (0)	1 (33.3)	2 (66.7)
Scratching	**1 (0.3)**	1 (100)	0 (0)	0 (0)
Splash	**10 (3.4)**	2 (20.0)	2 (20.0)	6 (60.0)
Unknown object	**3 (1.0)**	3 (100)	0 (0)	0 (0)
Median time between exposure and reporting (hrs), range; (n=277)	**2.0, 0.05-144**	2.0, 0.08-144	2.0, 0.16-120	2.0, 0.5-72

Abbreviations: HCWs, health care workers; HCSs, health care students; KBTH, Korle-Bu Teaching Hospital; SME, surgical/medical emergency; OPD, outpatient department.

[a]Column percentages within rows.

[b]Row percentages within supercolumns.

a sharp object and 10 (3.9%) exposures occurred from blood splash. Percutaneous exposures were the most common exposure type across all job categories. Of the 271 percutaneous exposures, 270 (99.6%) were injuries from either needle-sticks (246 reports) or cannulae (24 reports). Trend analysis showed that over the 6-year period of the study (2005-2010), percutaneous exposure decreased significantly (p=0.026), while mucocutaneous exposures increased (p=0.026; Figure 2). Of the 295 exposure source patients, it was possible to conduct HIV tests on 247. Forty-eight exposure source patients were unavailable or the data on their HIV status could not be ascertained. Of those tested (n=247), 88 were HIV positive, giving the HIV-sero-positivity among the exposure source tested in this study as 35.6%. Trend analysis showed that the proportion of exposure sources with HIV-positive status did not change significantly (p=0.340) during the study period (Figure 2).

Table 2. Incidence of exposures per 100 P-Y of HCWs/HCSs at KBTH in Accra, Ghana.

Profession (number employed)	PEP exposed	Number of P-Y	Total exposure per 100 P-Y	RR	95% CI	p-value
Nurses (n=1200)	116	7200	**1.61**	**1.00**	**Reference**	
Ward Attendants (n=80)	31	480	6.46	4.01	2.90-5.55	<0.001
Laboratory staff (n=100)	18	600	3.00	1.86	1.18-2.93	0.008
Physicians (n=550)	95	3300	2.88	1.79	1.40-2.30	<0.001
Healthcare students (n=3330)	35	8400	0.42	0.26	0.18-0.37	<0.001

Abbreviations: CI, confidence interval; HCWs, health care workers; HCSs, health care students; KBTH, Korle-Bu Teaching Hospital; RR, relative risk; P-Y, person years

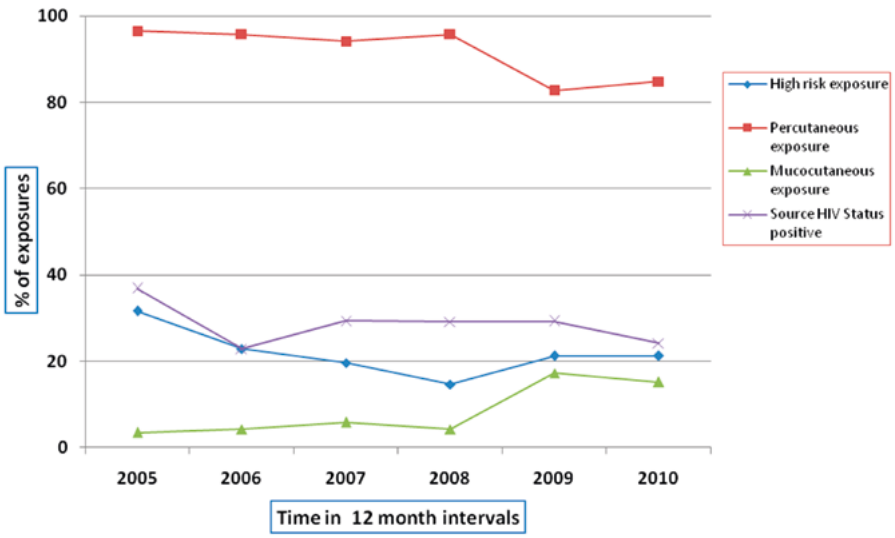

Figure 2. Trends over time in exposure types and source of HIV status at KBTH in Accra, Ghana. KBTH indicates Korle-Bu Teaching Hospital

Risk Assessment System and Exposure Management

Using the RAS, the clinical assessment team graded 65 (22.0%) cases of the 295 reported exposures as being of high-risk exposure, 65 (22.0%) as medium-risk exposures, and 165 (55.9%) as low-risk exposures (Figure 3). Laboratory investigations later confirmed that as many as 57 (87.7%) of the graded 65 high-risk cases were cases with exposure source being HIV positive, 1 (1.5%) exposure source was HIV negative, and 7 (10.8%) were of unknown HIV status because of unknown exposure sources (Figure 3). A majority (55 reports, 84.6%) of the high-risk exposures were percutaneous (Table 1). The incidence of high-risk exposures was 0.33 of 100 P-Y (n= 65); 60.0% occurred during a procedure of disposing of a needle and 24.6% occurred during a canula insertion. The incidence of high-risk exposures did not change significantly (P = 0.220) during the study period (Figure 2).

A total of 289 exposures were administered PEP, with 224 exposures receiving dual therapy and 64 receiving triple therapy. Of the 65 exposures who received triple therapy, 64 belonged to the "high"-risk category, while 64 of 65 and 160 of 165 exposures belonged to the "medium"- and "low"-risk categories, respectively. Six exposures (2.0%) were not administered any medication because the reportage was more than 72 hours after the incident. The RAS, however, categorized 5 of these exposures as low risk and 1 case as medium risk.

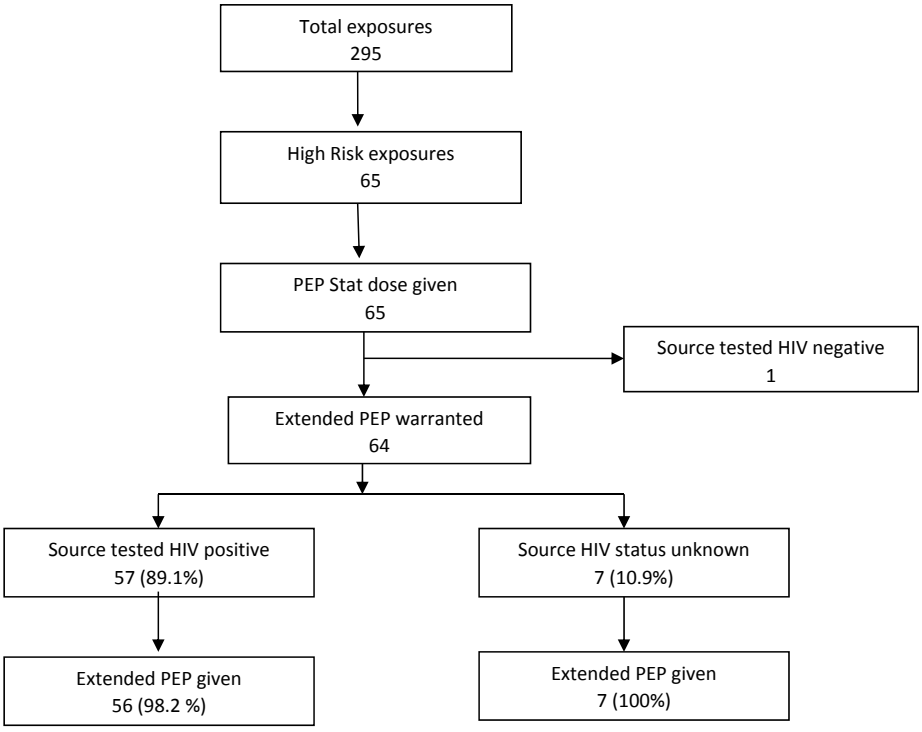

Figure 3. The postexposure prophylaxis (PEP) expanded regimen use: clinical decisions

Adherence to Follow-Up Testing

Adherence to follow-up testing for HIV status in the 289 patients administered PEP was 87.2% (252 exposures) at the first follow-up testing schedule of 6 weeks and 75.1% (217 exposures) during the second follow-up testing schedule of 3 months. The last follow-up testing schedule of 6 months recorded 62.6% (181) of the exposed HCWs/HCSs. Further analysis indicated that there was no statistical difference (p=0.05) between the various categories of exposed HCWs/HCSs in terms of the rate of adherence to the 3 follow-up testing schedules. Feedback from each of the follow-up testing schedules showed no documented or reported sero-conversion to HIV.

DISCUSSION

In this study, 295 occupational exposures to HIV occurred in 260 HCWs and 35 HCSs with each exposed HCW/HCS being recorded as reporting once for the PEP service during the study period. It is, however, unknown whether after the 6-month period each person in the cohort had any further occupational exposure to HIV or sought PEP elsewhere. This information is clearly beyond the scope of this study.

Despite the 62.6% level of follow-up testing adherence after the 6th month, which compares with other similar studies [12, 13], results from this study indicate that the PEP service provided in the KBTH as a policy intervention over the period under review was beneficial to HCWs and students who were exposed occupationally as none of the exposed followed-up HCW/HCS sero-converted to HIV positive. Additionally, it offered the platform for exposed HCWs/HCSs to gain confidence in the availability of adequate, effective, and efficient means of addressing occupational exposures to HIV, which otherwise would have lead to tremendous fear, anxiety, and stress, which are likely to have negative effect on them and their families. The RAS deployed as part of PEP in the teaching hospital seems to have led to the effectiveness of the service. This finding, while is consistent with similar studies in Nigeria [7], India [14], and Kenya [15], also reemphasizes the use of dual/triple triple therapy over monotherapy (ZDV) as the latter has being implicated in 21 instances of PEP failure to prevent HIV sero-conversion in the United States [16]. The results of this study also indicated that of the 65 cases classified as high risk, 57 (87.9%) of the source patients turned out to be HIV positive, with 7 (10.8%) of unknown source, further confirming the real-life usefulness of the triaging system. This RAS is a necessary complementary tool in resource-constrained settings where there is limited availability of HIV rapid diagnostic test kit at all service delivery points meaning that at the site of injury there may be no rapid diagnostic test to tell whether the source patient was HIV positive or not. This, coupled with the time lapse between injury and the availability of the results of laboratory investigation of the HIV status of the source patient (usually more than 72 hours—the time limit for PEP initiation), makes it imperative to have a tool, like the RAS, to be used to complement the decision of exposed HCWs/HCSs eligible for PEP and also to decide on those who receive short-course versus expanded PEP.

Using the RAS being implemented in the KBTH, 6 (2.03%) of the exposures reported outside the 72-hour window during which PEP is known to be effective and were not therefore administered PEP. These 6 HCWs were, however, counselled and advised to check their status and that of the source patient as appropriate and feasible. Although no sero-conversion has been reported by these exposed individuals to the hospital authorities, this study being a retrospective one was unable to definitely rule out any sequelae in these due to confidentiality and ethical considerations and issues. This observation is worrying and calls for increased education and advocacy efforts of all HCWs and HCSs to ensure that every single one of them is aware of the provision of PEP in the teaching hospital and to seek the intervention within the stipulated time.

Although results from other studies [17-19] have shown that interns and students are more at risk than senior staff members, results from this study indicate that HCSs appeared to be the group with the least risk. This information is, however, limited by not capturing the various grades of the HCWs. However, one of the most interesting findings of this study is the relative risk for PEP among the different categories of HCWs/HCSs. Although nurses, by simple count, reported more exposures than the other HCWs, ward attendants recorded the highest incidence rate of 6.46 of 100 P-Y, which was far higher than the overall incidence rate of 1.48 of 100 P-Y for all HCWs/ HCSs. In addition, ward attendants were found to be 4 times at greater risk of getting an injury requiring PEP than nurses. Although reasons which can be advanced for this observation include lack of tools and facilities, huge numbers of patients, pressure from other health workers, naivety, inadequate education, and poor adherence to procedures and safety practices which are counterproductive to the delivery of an effective health service, this delicate group of HCWs should in future be targeted for specific education on universal requirements for protection. Future studies must explore the reasons for this observation and corrected.

The observation that 5 departments, namely, departments of surgery, child health, surgical/medical emergency and trauma, obstetrics and gynaecology, and internal medicine in the reported order recorded more than 70.0% of the total reported exposures needs to be studied further and the reasons for departmental differences need to be ascertained and addressed.

Results from this study indicated that as many as 84.6% of the high-risk graded exposures were due to injuries from needle-stick or cannula, This result, although similar to other PEP studies [17, 18, 20], underlines the need for the use of safer medical devices (e.g., needleless systems and sharps with engineered sharps-injury protections) to reduce the occurrence of especially high risk to contaminated sharps. In fact, certain clinical practices such as recapping used needles have been documented to be related more to the likelihood of needlestick injuries and thus the practices have been condemned [21-23]. This preventive measure, however, poses a challenge in terms of cost on the already resource-constrained health care delivery system in Ghana, which nevertheless must be addressed to reduce health care occupational injuries.

Results from the study also show that a vast majority (91.9%) of the reported exposures during the entire study period were percutaneous. However, trend analysis revealed that the proportion of percutaneous injuries reduced significantly over the 6-year period, while mucocutaneous injuries rose steadily although the relative numbers remained below 20% of all exposures. This may be due to awareness by HCWs/HCSs in reporting all types of exposures including mucocutaneous exposures, which were previously overlooked because of intact skin. Similar trend analysis did not point to any decreasing number of retro-positive source patients or high-risk exposures, which could have reflected the steady decrease in the HIV prevalence rate from an earlier 3.7% in 2000 to 1.9 in 2010 but which has moved up to 2.1 in the last sentinel survey report on Ghana [10].

Notwithstanding the significant findings and the particular usefulness of the retrospective type of study design for occupational exposures, in terms of less time and cost-effectiveness, a possible limitation is the absence of data on the number of years of experience and grade of the various categories of the exposed HCWs, which may be a potential confounding factor. Additional possible limitation of the current study is the number or proportion of HCW who did not seek care after PEP. Although the present study did not actually examine that, it will be reasonable to conduct such a survey as soon as possible to complement the outcome of the present study. A simple survey to assess the knowledge and utilization of PEP among HCW at the KBTH should suffice. In addition, the inability to capture the viral hepatitis status of exposed HCW/HCS and that of source patients limited the provision of PEP for occupational exposure to anti-HIV medicines only. A possible reason for this is the challenge of paying out of pocket for hepatitis screening. However, all exposed HCWs and HCSs were encouraged to check their hepatitis status, and if negative, hepatitis vaccine was recommended. Furthermore, the study was based in one, albeit a major, institution in Ghana, and the findings cannot be generalized to the whole country. Although the KBTH, which is a tertiary referral hospital, has the largest number of HCWs/HCSs in Ghana and also receives referrals for PEP from other hospitals that do not offer PEP services, a more specific, purposive, and well-funded survey is required to obtain the national picture. Data available, which is collated by the National AIDS and STI Control Program of Ghana (NACP), included only the number of exposures and types of ART used. An overview of PEP service nationwide would provide useful findings that could be used to guide a national policy on the management of occupational and non-occupational exposures to body fluids.

CONCLUSIONS

The present study shows that the RAS as a complement to the standard HIV rapid diagnostic kit at the KBTH for providing PEP is effective in identifying and classifying high-risk exposures for appropriate management. Of the 289 exposures of HCWs/HCSs who were provided PEP, only 181 (62.6%) adhered completely to the follow-up testing schedule, and none sero-converted at the last test after 6 months. The 289 exposed HCWs/HCSs reported for PEP within 72 hours of exposure and only 6 (2%) reported after more than 72 hours of exposure.

The study also suggests that despite resource constrains in Ghana, PEP services should continue to be encouraged for all injured HCWs/HCSs. Efforts should be made to reduce underreporting, and targeted education should be implemented for ward attendants and other HCWs especially on the avoidance of percutaneous type injuries. The introduction of safer medical devices for procedures could also help avoid some of the injuries requiring a PEP service.

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Chapter 2.2

ADVERSE EVENTS AND ADHERENCE TO HIV POST-EXPOSURE PROPHYLAXIS: A COHORT STUDY AT THE KORLE-BU TEACHING HOSPITAL IN ACCRA, GHANA

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ABSTRACT

Background

There is strong evidence that post-exposure prophylaxis (PEP) with antiretroviral drugs in the timely management of occupational exposures sustained by healthcare workers decreases the risk of HIV infection and PEP is now widely used. Antiretroviral drugs have well documented toxicities and produce adverse events in patients living with HIV/AIDS. In the era of "highly active antiretroviral therapy", non-adherence to treatment has been closely linked to the occurrence of adverse events in HIV patients and this ultimately influences treatment success but the influence of adverse events on adherence during PEP is less well studied.

Methods

Following the introduction of a HIV post-exposure prophylaxis program in the Korle-Bu Teaching Hospital in January 2005, the incidence of adverse events and adherence were documented in occupationally-exposed healthcare workers (HCWs) and healthcare students (HCSs). Cohort event monitoring was used in following-up on exposed HCWs/HCSs for the two study outcomes; adverse events and adherence. All adverse events reported were grouped by MedDRA system organ classification and then by preferred term according to prophylaxis regimen. Adherence was determined by the completion of prophylaxis schedule. Cox proportional regression analysis was applied to determine the factors associated with the cohort study outcomes. Differences in frequencies were tested using the Chi square test and $p < 0.05$ was considered statistically significant.

Results

A total of 228 exposed HCWs/HCSs were followed up during the study, made up of 101 exposed HCWs/ HCSs administered lamivudine/zidovudine (3TC/AZT) for 3 days; 75 exposed HCWs/HCSs administered lamivudine/zidovudine (3TC/AZT) for 28 days; and 52 exposed HCWs/HCSs administered lamivudine/zidovudine/lopinavir-ritonavir (3TC/AZT/LPV-RTV) for 28 days. The frequency of adverse events was 28 % (n = 28) in exposed HCWs/HCSs administered 3TC/AZT for 3 days, 91 % (n = 68) in exposed HCWs/HCSs administered 3TC/AZT for 28 days and 96 % (n = 50) in exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28 days. Nausea was the most commonly reported adverse events in all three regimens. Adherence was complete in all exposed HCWs/HCSs administered 3TC/AZT for 3days, 56 % (n = 42) in exposed HCWs/HCSs administered 3TC/AZT for 28 days and 62 % (n = 32) in exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28 days. In the Cox regression multi-variate analysis, exposed HCWs/HCSs administered 3TC/AZT for 3 days were 70 % less likely to report adverse events compared with exposed HCWs/HCSs administered 3TC/AZT for 28 days (Adjusted HR = 0.30 [95 % CI, 0.18-0.48], $p < 0.001$). Exposed HCWs/HCSs administered 3TC/AZT for 3 days were 75 % more likely to adhere to the schedule compared

with exposed HCWs/HCSs administered 3TC/AZT for 28 days (Adjusted HR = 1.75 [95 % CI, 1.16-2.66], p = 0.008).

Conclusion

The intolerance to adverse events was cited as the sole reason for truncating PEP, thereby indicating the need for adequate, appropriate and effective counselling, education, active follow-up (possibly through mobile/phone contact) and management of adverse events. Education on the need to complete PEP schedule (especially for exposed HCWs/HCSs on 28-day schedule) can lead to increased adherence, which is very critical in minimizing the risk of HIV sero-conversion. The present results also indicate that cohort event monitoring could be an effective pharmacovigilance tool in monitoring adverse events in exposed HCWs/HCSs on HIV post-exposure prophylaxis.

BACKGROUND

2.2

There is evidence that post-exposure prophylaxis (PEP) with antiretroviral drugs in the timely management of occupational exposures sustained by healthcare workers (HCWs) decreases the risk of HIV infection and this type of approach is now widely used [1, 2]. A case control study among HCWs showed that post-exposure uses of zidovudine after percutaneous exposure to HIV infected blood was associated with a reduction of the risk of HIV infection by about 81 % [3, 4].

In HIV-infected patients, combination regimens have proven to be superior to monotherapy regimens in reducing viral load [5, 6]. Thus, a combination of drugs with activity at different stages in the viral replication cycle theoretically may offer a greater preventative effect in PEP, particularly for occupational exposures. This is supported by clinical evidence that the use of dual or triple antiretro-viral drugs in PEP can prevent sero-conversion by as much as 80 % [7]. However, speed of thought and action is crucial as the window of opportunity to prevent systemic viral dissemination is narrow. Based on these findings, the WHO recommended the use of combination regimens (dual/triple) to prevent HIV sero-conversion in PEP programs which was adopted and adapted by the National HIV/AIDS Control Program (NACP) for use in Ghana [8]. However, the decision to initiate PEP must take into account the potential benefit of preventing infection versus the risk of toxicity from the medications used.

Antiretroviral drugs (ARVs) have well documented toxicities and produce adverse events in patients living with HIV/AIDS. These adverse events have been reported in several studies involving cohorts of patients with incidence rates as high as 54 % being reported in some instances [9, 10]. In the era of "highly active anti-retroviral therapy" (HAART), non-adherence to treatment has been closely linked to the occurrence of adverse events in HIV patients and this ultimately influences treatment success [11–14]. HAART is also used for PEP but for a shorter duration of maximally 28 days compared with HIV patients who are generally on life-long medication. However, several studies indicate a higher frequency of reported adverse events in PEP patients who receive multidrug regimens compared with HIV positive patients taking similar or same medication for HIV management [15–22]. This frequency is higher among PEP patients who received triple therapy compared with those who received dual therapy [15, 21] but the rate of discontinuation of PEP was not significantly different between the two PEP therapy groups [21].

With the introduction of HAART, there have been considerable changes in the administered ARV cocktail which comes along with its own adverse events and adherence issues. The use of ARVs in PEP has shifted from the administration of single-drugs like zidovudine to multi-drug regimens involving dual or triple therapy with their associated issues of adverse events and adherence. Very few studies on adverse events and adherence in exposed HCWs/HCSs administered PEP has been conducted in developing countries, hence results from resource-limited settings like the Korle-Bu Teaching Hospital (KBTH) in Accra, Ghana is useful for an effective implementation and education of HCWs on PEP in these settings. Such studies also go a long way to aid program design and national policy in relation to PEP.

The KBTH in Ghana with a workforce of about 1930 HCWs and 3330 healthcare students (HCSs), attends to over 3000 patients daily and also provides HAART services to over 20,000 HIV patients. In 2003, the National AIDS/STI Control Program (NACP) in Ghana provided guidelines on the provision of PEP in all sites that offer clinical care to patients living with HIV including KBTH, one of the four pilot sites for ART delivery at the time. KBTH has since then been offering HAART services to clients regularly.

This study utilizes cohort event monitoring to follow exposed HCWs/HCSs for adverse events and adherence to PEP during a PEP service between January 2005 and December 2010. Cohort-event monitoring (CEM), a prospective and observational cohort study is an adaptation of prescription-event monitoring and it involves actively following up on patients within a defined time-frame for reports of adverse events [23]. CEM employs the technique of actively collecting adverse events reports from patients, mostly by mobile phone calls or, in some cases, direct home visits. Collection of safety data using mobile phones is very appropriate for resource-limited settings like Ghana where the penetration of mobile telephony is high.

METHODS

Setting

This study was a prospective cohort analysis of HCWs/ HCSs administered PEP at the KBTH in Accra, the premier tertiary referral hospital in Ghana, during the period of January 2005 to December 2010. A team of healthcare professionals made up of medical and pharmacy personnel were responsible for providing PEP service to exposed healthcare workers using an in-house risk assessment system previously described [24] as well as guidelines based on the recommendations of the US Centers for Disease Control and Prevention (CDC) [25]. A risk assessment is done considering the type of injury, the volume of fluid involved, the type of instrument involved (e.g. hollow-bore needle, solid needle etc.) the HIV status of the source patient, the HIV viral load of the source patient and the circumstances surrounding the injury (the depth and extent of injury) as per the national guidelines. This is done on a one-on-one basis for individuals presenting following an exposure. Based on the results of the assessment, a decision is made as to the level of risk of the exposure and the appropriate HIV PEP to be administered according to local guidelines. HCWs/HCSs with exposures assessed as high risk were administered either lamivudine/zidovudine/ lopinavir-ritonavir (3TC/AZT/LPV-RTV) (triple therapy) for 28 days or lamivudine/zidovudine (3TC/AZT) (dual therapy) for 28 days. HCWs/HCSs with exposures assessed as medium or low risk were administered either lamivudine/zidovudine (3TC/AZT) (dual therapy) for 28 days or lamivudine/zidovudine (3TC/AZT) for 3 days. However in some exceptional cases, some HCWs/HCSs with exposures assessed as low/medium risk were administered 3TC/ AZT/LPV-RTV for 28 days on their insistent request. Figure 1 outlines the algorithm used in the risk assessment of exposures.

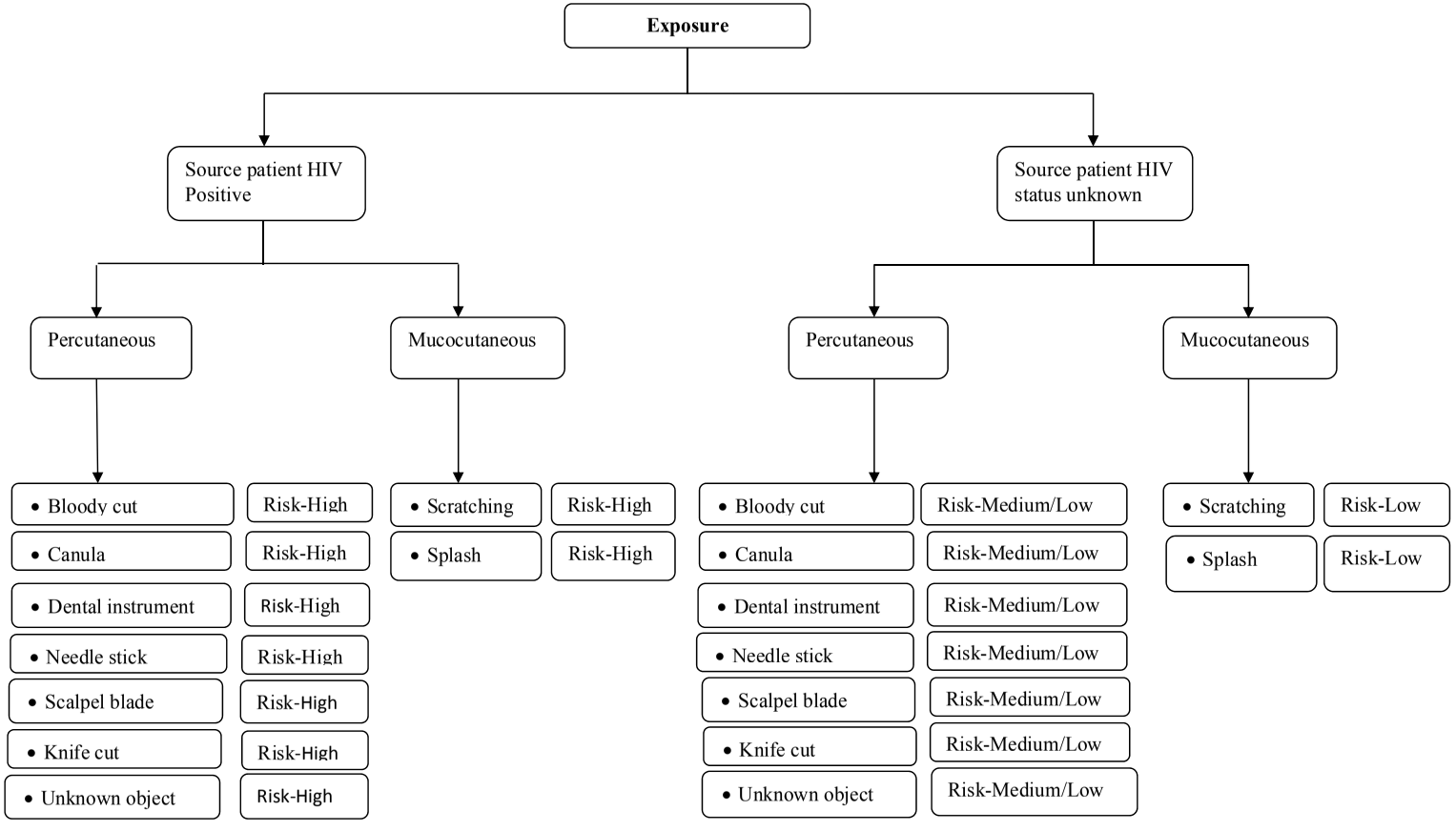

Figure 1. Algorithm used in determining the level of risk of exposures

Data collection

The procedures and criteria for the administration of PEP and collection of data (age, gender, HIV status of exposure source, means of exposure, type of exposure, risk assessment, profession, duration of exposure and department where the HCW/HCS belongs) have been described in a previous paper [24]. Exposed HCWs/HCSs were administered either lamivudine/zidovudine (3TC/AZT) (dual therapy) for 3 or 28 days (depending on the outcome of the risk assessment made) or lamivudine/zidovudine/lopinavir-ritonavir (3TC/AZT/LPV-RTV) (triple therapy) for 28 days. Active follow-up on exposed HCWs/HCSs were for two outcomes: a) HIV-testing schedule for possible sero-conversion (at 6 weeks, 3 months and 6 months) and b) adverse events and adherence. Outcome of the follow-up for HIV-testing schedule has been described previously [24].

Active follow-up for adverse events and adherence to prophylaxis schedule were performed by trained research assistants through telephone contact on days 3 and 10 after drug dispensing for those on the 3-day schedule and on days 3, 10, 20, 28 and 35 after drug dispensing for those on the 28 days schedule. In addition to the active follow-up, exposed HCWs/HCSs were asked to report events of medical concern (literally "anything that worries you") at any time during the follow-up period, noting especially the following signs; fever, rash, lymphadenopathy, dark-coloured urine, sore throat and bruising or bleeding from any part of the body. A structured questionnaire, interview guide was used to collect data from exposed HCWs/HCSs. Event data on adverse events was first recorded according to how the patient described the event (verbatim) and then reviewed qualitatively and coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 13.1) terminology. All adverse events reported were grouped by MedDRA system organ classification (SOC) and then by preferred term (PT) according to prophylaxis regimen. It is important to note that unlike some CEM studies, the presence of adverse events prior to treatment initiation was not undertaken. All adverse events solicited post-treatment were new events that could conceivably be associated with PEP though no formal case-causality assessment was carried out on the individual reports.

Adherence was determined by the completion of prophylaxis schedule assessed during the follow-up period by the use of a questionnaire. Non-adherence was defined as the inability to complete all the 3 days of the prophylaxis schedule for exposed HCWs/HCSs on the 3-day schedule and all the 28 days for exposed HCWs/HCSs on the 28-day schedule as prescribed.

Data management and analysis

Each exposed HCW/HCS was given a unique study code which was used in data storage and management relating to that HCW/HCS. Data were double entered, cleaned and managed using Microsoft Access (Microsoft Corporation, Redmond, Washington) and analysed using SPSS version 19 (IBM, Armonk, New York). Data were expressed as frequencies and percentages for categorical variables. Differences in frequencies and proportions were tested using

the chi square test. The primary outcomes of interest were "adverse events" and "adherence". Cox proportional regression analysis was applied to determine the factors associated with adverse events/adherence and reported as a crude hazard ratio in the univariate analysis. Variables significantly associated with adverse events or adherence in the univariate analysis (at $p < 0.10$) were adjusted for in the multivariate analysis and reported as an adjusted hazard ratio. $P < 0.05$ was considered statistically significant.

Ethics

The study was approved by the Ethical and Protocol Review Committee of the University of Ghana Medical School [MS-Et/M.6-P.5.3/2009-10].

RESULTS

Exposure information and characteristics of HCWs during reporting and HIV PEP administration

Results from Fig. 2 indicate that out of a total of 280 HCWs/HCs who reported for the PEP service during the study period, 145 (51.8 %) exposed HCWs/HCSs were administered 3TC/AZT for 3 days of which 101 were successfully followed up, 82 (29.3 %) exposed HCWs/HCSs were administered 3TC/AZT for 28 days of which 75 exposed HCWs/HCSs were successfully followed up and 53 (18.9 %) exposed HCWs/HCSs were administered 3TC/AZT/LPV-RTV for 28 days of which 52 exposed HCWs/HCSs were successfully followed up. A total of 16 exposed HCWs/HCSs (11 exposed HCWs/ HCSs administered 3TC/AZT for 3 days and 5 exposed HCWs/HCSs administered 3TC/AZT for 28 days) truncated their regimen schedule when the source patient tested HIV negative. The lost to follow-up (LFU) proportion among exposed HCWs/HCSs administered 3TC/AZT for 28 days was significantly lower ($p < 0.001$) compared with those administered 3TC/AZT for 3 days, but not significantly different ($p = 0.832$) from exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28 days. Over 80 % of the exposed HCWs/HCSs reported their exposure within 24 h and the median time between

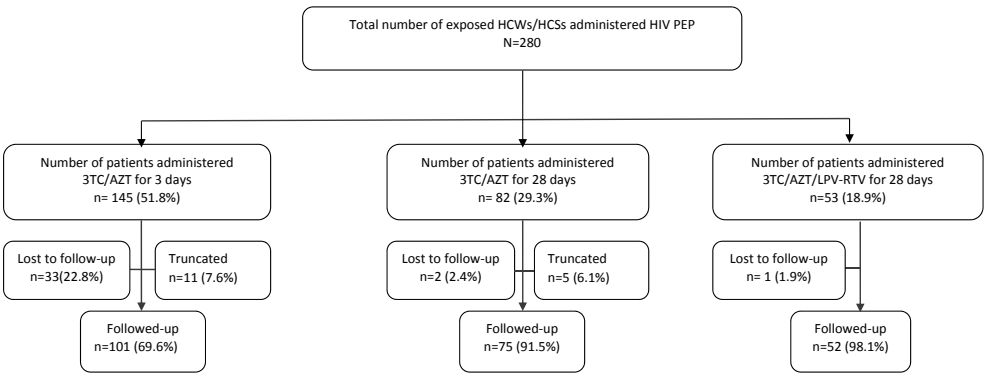

Figure 2. Distribution of exposed HCWs/HCSs administered PEP by regimen

exposure and reporting was 2.0 h in both HCWs and HCSs. Follow-up for HIV testing was done at 6 weeks, 3 months and 6 months after exposure/HIV PEP administration and none of the HCWs/HCSs followed-up sero-converted.

Table 1 show characteristics of the HCWs/HCSs administered the HIV PEP regimen. The female population constituted 68 % (n = 99) of exposed HCWs/HCSs administered 3TC/ AZT for 3-days, 50 % (n = 41) of exposed HCWs/HCSs administered 3TC/AZT for 28 days and 53 % (n = 28) of those administered 3TC/AZT/LPV-RTV for 28 days. The 18–30 years age category represented the largest number of HCWs/HCSs administered all the three PEP regimens (82 % in exposed HCWs/HCSs administered 3TC/AZT for 3-days, 60 % in exposed HCWs/HCSs administered 3TC/AZT for 28 days and 70 % in exposed HCWs/HCSs administered 3TC/AZT/ LPV-RTV for 28 days). Whilst risk assessment results for most of the exposed HCWs/ HCSs administered 3TC/ AZT for 3-days were low (86 %, n = 125), the majority of exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28 days risk assessment results was high (83 %, n = 44). The majority of exposed HCWs/HCSs administered 3TC/ AZT for 28 days risk assessment results were either low risk (35 %, n = 29) or medium risk (48 %, n = 39). A vast majority of the reported exposures in general were percutaneous (93 %, n = 260) with needle stick injuries being the most reported means of exposure (85 %, n = 237).

Reporting of adverse events

Out of a total of 228 HCWs/HCSs administered HIV PEP and followed up, 146 (64 %) reported at least one adverse event made up of three spontaneous reports and 143 reports from active surveillance. The proportion of those who reported at least one adverse event was significantly higher ($p < 0.001$) in exposed HCWs/HCSs administered 3TC/AZT for 28 days (n = 68, 91 %) compared with exposed HCWs/HCSs administered 3TC/AZT for 3 days (n = 28, 28 %) but not significantly different ($p = 0.236$) from exposed HCWs/HCSs administered 3TC/ AZT/LPV-RTV for 28 days (n = 50, 96 %).

Table 2 shows the Cox regression analyses to determine factors associated with the occurrence of adverse events. In the univariate analysis, gender, profession, age category and type of exposure were not associated with the reporting of adverse events. The outcome of the risk assessment done prior to drug administration (low, medium or high) was associated with adverse events in the univariate but not associated when adjusted for other variables in the multivariate analysis. The duration of drug regimen administered was associated with the reporting of adverse events in both the univariate and multivariate analysis. For exposed HCWs/HCSs administered the same drug regimen (3TC/AZT) for different durations, those administered 3TC/AZT for 3 days were 70% less likely to report an adverse event compared with those administered 3TC/AZT for 28 days (Adjusted HR=0.30 [95 % CI, 0.18-0.48], $p < 0.001$) (Table 2). There was no significant difference ($p = 0.817$) in the reporting of adverse events between exposed HCWs/ HCSs administered 3TC/AZT for 28 days and exposed HCWs/ HCSs administered 3TC/AZT/LPV-RTV for 28 days in the multivariate analysis.

Table 1. Baseline characteristics of 280 HCWs/HCSs reporting occupational exposures and administered HIV post-exposure prophylaxis at an urban teaching hospital in Accra, Ghana, 2005–2010

	Drug regimen administered		
Characteristics	**3TC/AZT-3 days N=145 n, %[1]**	**3TC/AZT-28 days N=82 n, %[1]**	**3TC/AZT/LPV-RTV -28 days N=53 n, %[1]**
Gender			
Male	46 (31.7)	41(50.0)	25 (47.2)
Female	99 (68.3)	41(50.0)	28 (52.8)
Age category (yrs)			
18-30	119 (82.1)	49 (59.8)	37 (69.8)
31-40	21 (14.5)	24 (29.3)	10 (18.9)
41-50	3 (2.1)	5 (6.1)	5 (9.4)
> 50	2 (1.4)	4 (4.9)	1 (1.9)
Outcome of risk assessment of exposure			
Low	125 (86.2)	29 (35.4)	5 (9.4)
Medium	20 (13.8)	39 (47.6)	4 (7.6)
High	-	14 (17.1)	44 (83.0)
Profession			
Medical Doctors	40 (27.6)	27 (32.9)	22 (41.5)
Nurses	64 (44.1)	26 (31.7)	19 (35.8)
Laboratory Staff	4 (2.8)	8 (9.8)	5 (9.4)
Ward Attendants	13 (9.0)	13 (15.9)	4 (7.5)
Healthcare Students	24 (16.6)	8 (9.8)	3 (5.7)
Type of exposure			
Mucucutaneous	7 (4.8)	3 (3.7)	10 (18.9)
Percutaneous	138 (95.2)	79 (96.3)	43 (81.1)
Year of exposure			
2005	26 (17.9)	14 (17.1)	12 (22.6)
2006	30 (20.7)	10 (12.2)	4 (7.5)
2007	23 (15.9)	15 (18.3)	10 (18.9)
2008	24 (16.6)	16 (19.5)	6 (11.3)
2009	27 (18.6)	15 (18.3)	15 (28.3)
2010	15 (10.3)	12 (14.6)	6 (11.3)
Means of exposure			
Bloody cut	1 (0.7)	1 (1.2)	1 (1.9)
Canula	4 (2.8)	2 (2.4)	16 (30.2)
Dental instrument	1 (0.7)	-	-
Needle stick	133 (91.7)	77 (93.9)	27 (50.9)
Scalpel blade	-	1 (1.2)	2 (3.8)
Scratching	1 (0.7)	-	-
Knife cut	1 (0.7)	-	-
Splash	2 (1.4)	1 (1.2)	7 (12.2)
Unknown object	2 (1.4)	-	-

[1]% are column percentages within each super row; 3TC=lamivudine; AZT=zidovudine; LPV-RTV=lopinavir-ritonavir.

Table 2. Factors associated with reported adverse events in 228 exposed HCWs/HCSs on HIV post-exposure prophylaxis

Characteristic	AE Status[1] Present	Absent	Crude Hazard ratio [95% CI]	p-value	Adjusted hazard ratio [95% CI]	p-value
Drug regimen						
3TC/AZT -28 days	68	7	1.00		1.00	
3TC/AZT-3 days	28	73	0.31 [0.20-0.48]	<0.001	0.30 [0.18-0.48]	<0.001
3TC/AZT/PI-28 days	50	2	1.06 [0.74-1.53]	0.752	1.06 [0.65-1.72]	0.817
Gender						-
Female	81	50	1.00			
Male	65	32	1.08 [0.78-1.50]	0.629		
Type of exposure						-
Percutaneous	131	80	1.00			
Mucocutaneous	15	2	1.42 [0.83-2.43]	0.197		
Age category (yrs)						-
18-30	101	60	1.00			
31-40	32	18	1.02 [0.69-1.52]	0.921		
41-50	8	2	1.21 [0.62-2.62]	0.508		
>51	5	2	1.14 [0.46-2.80]	0.777		
Risk assessment						
Low	51	63	1.00		1.00	
Medium	40	16	1.60 [1.06-2.42]	0.027	0.95 [0.61-1.49]	0.885
High	55	3	2.12 [1.45-3.10]	<0.001	0.97 [0.57-1.66]	0.922
Profession						-
Nurses	51	31	1.00			
HCS	14	10	0.94 [0.52-1.69]	0.832		
Laboratory Staff	15	1	1.59 [0.85-2.68]	0.162		
Medical Doctors	46	31	0.96 [0.65-1.43]	0.843		
Ward Attendants	20	9	1.11 [0.66-1.86]	0.695		

[1]N = 228, exposed HCWs/HCSs lost to follow (n = 36) and exposed HCWs/HCSs who truncated their schedule due to source patient testing HIV negative (n = 16) were excluded; 3TC = lamivudine; AZT = zidovudine; LPV-RTV = lopinavir-ritonavir; CI = confidence interval

Description of reported adverse events

The most frequently observed type of adverse event re-ported in all the three PEP regimens was gastrointestinal in nature (Table 3). Nausea, weakness, malaise and dizziness (17 %, 10 %, 6 % and 6 %, respectively) were the four most-commonly reported adverse events in exposed HCWs/ HCSs administered 3TC/AZT for 3 days. Exposed HCWs/ HCSs on 3TC/AZT for 28 days reported nausea (63 %), weakness (37 %), fatigue (28 %) and dizziness (27 %) as the four most reported adverse events. On the other hand, nausea, diarrhoea, vomiting and weakness (71 %, 65 %, 35 % and 31 %, respectively) were the four most commonly reported

adverse events in exposed HCWs/ HCSs administered 3TC/AZT/LPV-RTV for 28-days. Nausea was the most commonly reported adverse events in all three regimens. There were a total of five reports of rashes; two reports each in exposed HCWs/ HCSs administered 3TC/AZT for 3 days and 28 days and one report in an exposed HCW administered 3TC/ AZT/LPV-RTV for 28 days (Table 3).

There were three spontaneous reports of adverse events which ended up in hospitalisation but all recovered. The first was an exposed female HCW of 26 years administered 3TC/AZT/ LPV-RTV for 28 days who reported of dizziness, excessive flatulence, headache, nausea, vomiting, restlessness and dark pigmentation of finger & toe nails (which later came off) and was hospitalised for three days. The second case which resulted in hospitalisation for seven days involved a 29-year old exposed pregnant female HCW (in the first trimester of pregnancy) who reported of abdominal pains, profuse diarrhoea, fatigue, nausea and bleeding which later resulted in spontaneous abortion. The third case involved an exposed female HCW of 42 years who was administered 3TC/AZT for 28 days and reported of fatigue, headache and weakness which according to her resulted in a "near death" experience. She was hospitalised for three days. These three serious adverse events all involving females have been reported to the National Pharmacovigilance Centre at Ghana's Food and Drugs Authority.

Adherence to prophylaxis schedule

Complete adherence to PEP schedule was 77 % (n = 175) in this study. All the 53 PEP exposed HCWs/HCSs who defaulted in their 28-days prophylaxis schedule did so within 14 days of medication initiation. None of the exposed HCWs/HCSs on the 3-day schedule defaulted in medication adherence. Comparing the different PEP regimens administered, adherence to the prophylaxis schedule was significantly higher ($p < 0.001$) in exposed HCWs/ HCSs administered 3TC/AZT for 3-days (100 %, n = 101) compared with exposed HCWs/HCSs administered 3TC/ AZT for 28-days (56.0 %, n = 42) and exposed HCWs/ HCSs administered 3TC/AZT/LPV-RTV for 28-days (61.5 %, n = 32). However, there was no statistical difference ($p = 0.534$) in adherence proportion between ex-posed HCWs/HCSs administered 3TC/AZT for 28-days and exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28-days.

Table 4 shows the factors associated with adherence in both the univariate and multivariate Cox regression analysis. Gender, profession, outcome of risk assessment, type of exposure and age category was not associated with adherence in the univariate analysis. For the same drug regimen exposed HCWs/HCSs administered 3TC/ AZT for 3-days were 75 % more likely to adhere to the schedule compared with exposed HCWs/HCSs administered 3TC/ AZT for 28-days (Adjusted HR = 1.75 [95 % CI, 1.16-2.66], $p = 0.008$). There was no statistical significant difference in terms of adherence between exposed HCWs/HCSs administered 3TC/AZT for 28 days and exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28 days ($p = 0.660$).

In a separate analysis to determine the association between the two study outcomes (report of adverse events and adherence), exposed HCWs/HCSs who never reported of

Table 3. Preferred term within system organ classification of reported adverse events of exposed HCWs/HCSs on PEP

Adverse events by preferred term within system organ classification (n, %[1])	Total N=244	3TC/AZT-3 days N=112 n, %[1, 2]	3TC/AZT-28 days N=80 n, %[1, 2]	3TC/AZT/PI-28 days N=52 n, %[1, 2]
Gastrointestinal (n=122, 50.0%)				
Nausea	104 (42.6)	18 (16.1)	49 (61.3)	37 (71.2)
Diarrhoea	38 (15.6)	3 (2.7)	1 (1.3)	34 (65.4)
Vomiting	24 (9.8)	1 (0.9)	5 (6.3)	18 (34.6)
Loss of appetite	14 (5.7)	3 (2.7)	6 (7.5)	5 (9.6)
Abdominal pains	14 (5.7)	2 (1.8)	5 (6.3)	7 (13.5)
Anorexia	5 (2.0)	-	2 (2.5)	3 (5.8)
Dehydration	1 (0.4)	-	1 (1.3)	-
Bitter mouth	1 (0.4)	1 (0.9)	-	-
Constipation	1 (0.4)	-	1 (1.3)	-
Excessive flatulence	1 (0.4)	-	-	1 (1.9)
Abdominal discomfort	1 (0.4)	-	1 (1.3)	-
Hyper-salivation	1 (0.4)	-	-	1 (1.9)
Sore throat	1 (0.4)	-	-	1 (1.9)
Excessive spitting	1 (0.4)	-	1 (1.3)	-
Hunger pain	1 (0.4)	-	1 (1.3)	-
Systematic signs and symptoms (n=109, 44.7%)				
Weakness	55 (22.5)	11 (9.8)	28 (35.0)	16 (30.8)
Malaise	39 (16.0)	7 (6.3)	18 (22.5)	14 (26.9)
Dizziness	31 (12.7)	6 (5.4)	21 (26.3)	4 (7.7)
Fatigue	29 (11.9)	3 (2.7)	21 (26.3)	5 (9.6)
Feverish	5 (2.0)	-	2 (2.5)	3 (5.8)
General body pains	2 (0.8)	-	2 (2.5)	-

Table 3. (continued)

Adverse events by preferred term within system organ classification (n, %[1])	Total N=244	3TC/AZT-3 days N=112 n, %[1, 2]	3TC/AZT-28 days N=80 n, %[1, 2]	3TC/AZT/PI-28 days N=52 n, %[1, 2]
Neurological system (n=42, 17.2%)				
Headache	27 (11.1)	3 (2.7)	19 (23.8)	5 (9.6)
Restlessness	8 (3.3)	2 (1.8)	4 (5.0)	2 (3.8)
Insomnia	7 (2.9)	1 (0.9)	3 (3.8)	2 (3.8)
Drowsiness	6 (2.5)	1 (0.9)	2 (2.5)	3 (5.8)
Depression	1 (0.4)	-	1 (1.3)	-
Skin (n=9, 3.7%)				
Rashes	5 (2.0)	2 (1.8)	2 (2.5)	1 (1.9)
Itching	2 (0.8)	2 (1.8)	-	-
Alopecia	1 (0.4)	-	1 (1.3)	-
Dark pigmentation of finger & toe nails	1 (0.4)	-	-	1 (1.9)
Central/Peripheral nervous system (n=5, 2.0%)				
Eye pain	1 (0.4)	-	1 (1.3)	-
Leg pains	1 (0.4)	-	1 (1.3)	-
Neck pains	1 (0.4)	-	-	1 (1.9)
Pain in feet	1 (0.4)	-	-	1 (1.9)
Red eye	1 (0.4)	-	-	1 (1.9)
Hepatitis (n=2, 0.8%)				
Yellow eyes	1 (0.4)	-	1 (1.3)	-
Jaundice	1 (0.4)	-	-	1 (1.9)
Cardiac (n=1, 0.4%)				
Tightness in chest	1 (0.4)	-	1 (1.3)	-
Reproductive/gynaecological (n=2, 0.8%)				
Spontaneous abortion	1 (0.4)	-	-	1 (1.9)
Bleeding	1 (0.4)	-	-	1 (1.9)

[1]Percentages may add up to > 100; [2]% are percentages within each drug column; 3TC=lamivudine; AZT=zidovudine; PI= protease inhibitor; AE=Adverse event

Table 4. Factors associated with adherence in exposed HCWs/HCSs on HIV post-exposure prophylaxis

Characteristic	Adherence Status[1]		Crude hazard ratio		Adjusted hazard ratio	
	Adhered	Defaulted	[95% CI]	p-value	[95% CI]	p-value
Drug regimen						
3TC/AZT -28 days	42	33	1.00		1.00	
3TC/AZT-3 days	101	0	1.79 [1.25-2.56]	0.002	1.75 [1.16-2.66]	0.008
3TC/AZT/PI-28 days	32	20	1.10 [0.69-1.74]	0.688	1.02 [0.56-1.88]	0.938
Gender						
Female	102	29	1.00			
Male	73	24	0.97 [0.72-1.31]	0.824		
Age range						
18-30	129	32	1.00			
31-40	34	16	0.85 [0.58-1.24]	0.395		
41-50	6	4	0.75 [0.33-1.70]	0.489		
>51	6	1	1.07 [0.47-2.43]	0.872		
Risk assessment						
Low	103	11	1.00		1.00	
Medium	36	20	0.71 [0.49-1.04]	0.079	0.91 [0.60-1.39]	0.672
High	36	22	0.69 [0.47-1.00]	0.052	1.05 [0.56-2.00]	0.871
Type of exposure						
Percutaneous	165	46	1.00			
Mucocutaneous	10	7	0.75 [0.40-1.42]	0.382		
Profession						
Nurses	65	17	1.00			
HCS	19	5	1.00 [0.60-1.67]	0.996		
Laboratory Staff	9	7	0.71 [0.35-1.43]	0.335		
Medical Doctors	59	18	0.97 [0.68-1.38]	0.850		
Ward Attendants	23	6	1.00 [0.62-1.61]	0.998		

[1]N = 228, exposed HCWs/HCSs lost to follow (n = 36) and exposed HCWs/HCSs who truncated their schedule due to source patient testing HIV negative (n = 16) were excluded; 3TC = lamivudine; AZT = zidovudine; LPV-RTV = lopinavir-ritonavir; CI = confidence interval

adverse events were 57 % more likely to adhere to their medication schedule compared with exposed HCWs/HCSs who reported of at least one ad-verse event (HR = 1.57 [95 % CI, 1.17-2.11], p = 0.003). All the 53 exposed HCWs/HCSs who did not adhere completely to their PEP medication schedule cited adverse events as their reason for non-adherence.

DISCUSSION

The findings provide insight into the occurrence of adverse events and adherence to medication schedule in HIV negative HCWs/HCSs who presented for PEP at the KBTH between January 2005 and December 2010. The present results show that adverse events

are very common (1 in 10) in exposed HCWs/HCSs undergoing different regimens, more so with the 28-day regimens. Again, it showed that serious adverse events leading to hospitalization were common, occurring in this case at a frequency higher than 1 in 100 (3 serious adverse events in 228 exposed HCWs/HCSs). All the exposed HCWs/ HCSs who reported serious adverse events were females and were on 28 days regimen schedule. The importance of the duration of treatment on adverse events and adherence is starkly demonstrated by the fact that adverse events were low and adherence excellent in the 3 days regimen schedule whilst adverse events were more common and adherence varied between 56 and 62 % in the 28 days regimen schedule.

In this study exposed HCWs/HCSs administered PEP were allowed to describe their complaints in their own context before the use of the system organ class (SOC) classification to group the adverse events reported. In general, these exposed HCWs/HCSs administered PEP were not on other medications of note and therefore related these events to the anti-retroviral medications administered. The events reported did not exist prior to initiation of therapy. The present results indicate an overall adverse event frequency of 64 %, which is lower than the results of other studies where the frequency of adverse events was reported to be between 70 and 76 % [15, 18, 26]. However the reported high adverse events frequency of 96 % in exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV (triple therapy) for 28 days is comparable to reported adverse events frequency of also 96 % in PEP patients administered the same regimen of 3TC/AZT/LPV-RTV for 28 days in sexual assault survivors [27].

As expected, the adverse events reported were consistent with the product profiles (Summary of Product Characteristics-SmPC) of the PEP medications in use. The most frequently cited symptoms were gastrointestinal in nature; vomiting, diarrhoea, and nausea followed by neurological symptoms like headache, weakness and fatigue which is similar to results from other PEP studies [15, 18, 19, 28].

The study recorded three serious adverse events – all cases of hospitalisations following initiation of PEP. Worth noting was the case of dark pigmentation (hyper pigmentation) of finger and toe nails reported by a patient on 3TC/AZT/LPV-RTV for 28 days which incidentally has been reported in some other studies as a cutaneous adverse reaction of zidovudine (AZT), mostly in patients on chronic treatment of HIV [28]. The case of spontaneous miscarriage was recorded in a patient in the first trimester of pregnancy. The three anti-retroviral drugs involved (3TC/AZT/LPV-RTV) are classified as pregnancy category "C" and were used in as the benefits of the combination appeared to outweigh any potential risks. Whilst other causes for spontaneous abortion could not be ruled out in this patient, the occurrence of this event following intake of 3TC/AZT/LPV-RTV necessitates constant vigilance on the relationship between pregnancy outcomes and intake of the combination in order to generate enough evidence to support its continual use in pregnancy, especially during the first trimester whether used for PEP or for HAART. Both cases were also associated with severe diarrhoea and vomiting and the subjects were rehydrated, stabilized and discharged, with appropriate counselling to continue and complete the course of 28 days since their risk assessment were rated high. The third case of serious adverse event of fatigue, headache and weakness

involving an exposed female HCW of 42 years was also stabilized and discharged (after three days hospitalisation) with appropriate counselling to continue and complete the course of 28 days.

This study could not establish any association between the report of at least one adverse events and factors such as gender, age, profession, outcome of risk assessment and type of exposure in the multivariate analysis although other studies have associated adverse events with gender [17]. The present results showed that for the same type of drug regimen (dual therapy) administered as PEP, exposed HCWs/HCSs on the longer schedule (28 days) experienced more adverse than and were more likely to be non-adherent to treatment than those on shorter schedules. Even though other studies have shown an association of more frequent adverse events with triple therapy compared with dual therapy [1, 15, 21, 22], the present results rather indicate that the association may be due to the duration of therapy since there was no difference in frequency of adverse events when both the dual therapy (3TC/AZT) and triple therapy (3TC/AZT/LPV-RTV) were administered for 28 days. The association of longer duration of prophylaxis (28-days) to the reporting of adverse events may be due to the time to onset of adverse events as studies [15, 18] have shown adverse events to begin to appear from the fourth day of drug administration.

Results from this study indicate an overall adherence rate of 77 %. Although this adherence rate is far higher than reported in some studies [15, 26], it is comparable to other reports [19, 29]. Similar to the adverse events reportage, shorter therapy schedules of 3 days were associated with better (excellent in this study) adherence compared with the longer duration of 28 days. It has been shown that knowledge and proper communication of expected side effects of ARVs in patients leads to increased rate of adherence to the treatment [30]. The possibility of receiving either dual or triple therapy for 28 days depends on the outcome of the risk assessment which leaves no choice for the exposed HCW/HCS. Education and counselling are therefore very important in ensuring maximum adherence. The intolerability to adverse events was cited as the sole reason for truncating PEP, thereby indicating the need for adequate, appropriate and effective counselling, education, active follow-up (possibly through mobile/phone contact) and management of adverse events. Education on the need to complete PEP schedule (especially for exposed HCWs/HCSs on 28-day schedule) can lead to increased adherence which is very critical in preventing HIV sero-conversion. This may also reduce anxieties associated with the injuries. In addition, the need for monitoring and managing of adverse events may encourage completion of PEP schedule by HCWs who are exposed [31].

The use of the CEM technique in this study has led to the successful monitoring of adverse events and adherence to PEP schedule. This study has demonstrated that it is possible to effectively conduct an active safety monitoring of ARVs used in PEP in resource limited settings like the KBTH in Accra, Ghana. The safety data obtained from this CEM study are consistent with the safety profile expected for the medicines concerned. Since the tendency to passively/spontaneously report adverse events and adherence in HIV negative exposed HCWs/HCSs on PEP is generally low, CEM will become a key pharmacovigilance method

in resource-limited settings due to its ability to aid in rapid identification of signals and to effectively compare regimen and the effect of treatment type and duration on both adverse events and adherence.

Most of the exposed HCWs/HCSs were willing to be followed up by phone and loss to follow up was reasonably low compared to other studies in these settings. Although the inability to follow exposed HCWs/HCSs administered PEP beyond 6 months to monitor possible long term toxicities is a limitation, monitoring of long term toxicities was not the focus of the current study. Since laboratory tests for liver enzymes, full blood count, etc. were not conducted, it is not known to what extent the medicines might have caused abnormalities which could only be detected via laboratory testing. However, the relatively shorter period of 28 days given for PEP does not permit extrapolation of data to the identification of possible long-term toxicities that might have occurred if these products had been taken for long periods. The results cannot therefore be extrapolated to verify or refute known HAART induced toxicities like hepatitis or zidovudine-induced anaemia [32] which occur during the initial months of therapy in HIV-positive patients. Despite this, intensive laboratory monitoring during the period PEP should be encouraged and facilitated to identify all toxicities.

Although the results of this study cannot be necessarily generalized across HIV/AIDS treatment sites in Ghana or in West Africa and other resource-limited settings, the incidence of adverse events and non-adherence provides an insight into what to expect in such settings and this information could be used for patient education and the education of HCWs as PEP provision is scaled up. This study has shown the importance of focused cohort studies in generating important safety information in resource-limited settings where the spontaneous reporting ADR systems yield very little data and where healthcare systems e.g. absence of electronic health records and weak laboratory infrastructure, do not permit collection of safety data in any systematic manner. A possible limitation of the current study is the in-house medication adherence metrics used. Although medication adherence metrics are available including the one validated by Morisky et al. [33], none was used in this HIV PEP situation where exposed HCWs/HCSs may take the prophylactic medication for a maximum of 28 days. There is therefore the need to develop specific tools for measuring medication adherence in PEP whether short (3 days) or long (28 days) treatment periods are chosen.

CONCLUSIONS

In conclusion, it is possible to use active follow-up method via mobile phone calls to monitor both adverse events and adherence to prophylaxis regimen in HIV-negative PEP subjects. The study showed that adverse events to PEP are very common and could be severe or serious requiring hospitalization for management in some cases and that the nature and frequency of adverse events collected in the current study were consistent with available information on the use of those antiretroviral drugs. Much emphasis should be attached to follow-ups in order to advise and act promptly when issues arise. This study also indicated

the need for education of exposed HCWs/HCSs on the importance of complete adherence to HIV PEP in order to minimize the risk of HIV sero-conversion.

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Chapter 2.3

PRE-EXPOSURE PROPHYLAXIS FOR HIV PREVENTION: SAFETY CONCERNS

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ABSTRACT

Available evidence supports the efficacy of pre-exposure prophylaxis (PrEP) in decreasing the incidence of human immunodeficiency virus (HIV) infection among high-risk individuals, especially when used in combination with other behavioural preventive methods. Safety concerns about PrEP present challenges in the implementation and use of PrEP. The aim of this review is to discuss safety concerns observed in completed clinical trials on the use of PrEP. We performed a literature search on PrEP in PubMed, global advocacy for HIV prevention (Aids Vaccine Advocacy Coalition) database, clinical trials registry "http://www. clinicaltrials. gov" and scholar.google, using combination search terms 'pre-exposure prophylaxis', 'safety concerns in the use of pre-exposure prophylaxis', 'truvada use as PrEP', 'guidelines for PrEP use', 'HIV pre-exposure prophylaxis' and 'tenofovir' to identify clinical trials and literature on PrEP. We present findings associated with safety issues on the use of PrEP based on a review of 11 clinical trials on PrEP with results on safety and efficacy as at April 2016. We also reviewed findings from routine real-life practice reports. The pharmacological intervention for PrEP was tenofovir disoproxil fumarate/emtricitabine in a combined form as Truvada or tenofovir as a single entity. Both products are efficacious for PrEP and seem to have a good safety profile. Regular monitoring is recommended to prevent long-term toxic effects. The main adverse effects observed with PrEP are gastrointestinal related; basically mild to moderate nausea, vomiting and diarrhoea. Other adverse drug effects worth monitoring are liver enzymes, renal function and bone mineral density. PrEP as an intervention to reduce HIV transmission appears to have a safe benefit-risk profile in clinical trials. It is recommended for widespread use but adherence monitoring and real-world safety surveillance are critical in the post-marketing phase to ensure that the benefits observed in clinical trials are maintained in real-world use.

INTRODUCTION

At the end of 2015, the World Health Organization established that 36.7 million people were living with human immunodeficiency virus (HIV) with about 2.1 million becoming newly infected in the year [1]. With this high prevalence of HIV/acquired immune deficiency syndrome in the world, the World Health Organization related the urgency and importance of novel, effective and safe interventions in the prevention of HIV infection. This became necessary in that preventive behavioural messages on abstinence, faithfulness and condom use presented useful but limited impact as primary prevention on the spread of HIV. This challenge is observed especially among people at high risk because these protective measures were not applied consistently [2].

Human immunodeficiency virus continues to be a major public health problem and it has claimed more than 35 million lives so far. In 2015 alone, 1.1 million died from HIV-related causes worldwide [1]. The various management options for HIV including treatment, post-exposure prophylaxis and prevention of mother-to-child transmission have been integral in lowering HIV incidence, but reaching out to individuals at substantial risk owing to lifestyle practices required newer specific preventive approaches. Pre-exposure prophylaxis (PrEP) is a powerful tool in curbing the transmission of HIV infection [3], and it involves taking an antiretroviral (ARV) pill daily in addition to other preventive behavioural measures to prevent HIV infection. This is a protective mechanism used for individuals not diagnosed with HIV but who may be at substantial risk of becoming infected because of their lifestyle or as a partner in a sero-discordant relationship.

Results from clinical trials demonstrate the efficacy of PrEP, either used alone or in combination with other behavioural preventive methods, where it has been shown that PrEP can reduce the incidence of HIV by up to 86% [4, 5] or even more with strict adherence. Based on results and evidence from PrEP trials, the US Food and Drug Administration (FDA) on 16 July, 2012 approved Truvada [tenofovir (TDF) 300 mg/emtricitabine (FTC) 200 mg] (Gilead Sciences Inc., Foster City, CA, USA) as an effective medication for the prevention of HIV that could be sexually acquired [6, 7] and in all other types of possible HIV infection including injectable drug use. This was followed with guidelines for the provision of PrEP in clinical settings issued by the US Centers for Disease Control (CDC) and recently the World Health Organization also issued similar guidelines recommending PrEP as a prevention option for individuals at substantial risk for acquiring HIV [8, 9].

In the 2014 CDC guidelines, TDF alone based on positive results of substantial efficacy and safety in clinical trials with injectable drug use and heterosexual active adults was recommended as an alternative regimen for these populations, but not for men who have sex with men (MSM) because no efficacy studies were concluded as yet in the group. Again, the use of other antiretroviral medications for PrEP, either in place of or in addition to TDF/FTC or TDF alone is not recommended and finally the use of oral PrEP for sex activity-timed or non-continuous daily use is also not recommended [8]. The CDC also recommend in addition to regular follow-up testing for changes in HIV-negative status and adverse drug

monitoring including renal function before the initiation of PrEP and regularly while on preventive therapy. Routine bone mineral density (BMD) monitoring was not recommended by the CDC [8].

There are several challenges in the implementation and use of PrEP. These concerns include high costs, safety screening, toxicity arising from continuous use, adverse drug reactions, poor adherence, possible abuse and the fear of decreased condom use as an additional protective method [10, 11]. Poor adherence during PrEP is especially an important factor that may reduce effectiveness and lead to an increase in HIV infection rate with a possible development of HIV-resistant strains and subsequent transfer among the population. Factors that can affect adherence include adverse drug reactions (at regular doses) or toxicity (adverse drug reactions at probable high, intolerant doses or long-term use).

The ARV drugs presently recommended for oral PrEP are TDF or a combination of TDF/FTC. These medications have proven to be potent [12–14], have a favourable resistance profile and are claimed to have limited adverse effects, thus rendering them efficacious and safe for PrEP [14–17]. Some studies have also assessed the efficacy of a 1% vaginal gel formulation of TDF and found it to be effective in reducing HIV transmission by 39% [18]. Essential factors to be considered before using PrEP include a confirmed HIV-negative status with a normal renal function, a negative hepatitis B status, and absence of reduced BMD or a history of bone fractures, bone loss and osteoporosis [19, 20]. Recipients of PrEP also need to be tested on a minimum of a quarterly basis during follow-up to ensure they remain HIV negative, do not present with decreased estimated creatinine clearance levels or reductions in BMD [21]. The aim of this review is to describe and discuss safety concerns on the use of PrEP in the literature. Results from this review will contribute to the growing knowledge on the safety profile or use of PrEP.

METHODS

We performed a search of the literature on PrEP in PubMed (search date: 10 May, 2016), scholar.google (search date: 11 May, 2016), global advocacy for HIV prevention (Aids Vaccine Advocacy Coalition) database (search date: 12 May, 2016) and the clinical trials, "http://www.clinicaltrials.gov" (search date: 13 May, 2016), using combination search terms 'pre-exposure prophylaxis', 'safety concerns in the use of pre-exposure prophylaxis', 'truvada use as PrEP', 'guidelines for PrEP use', 'HIV pre-exposure prophylaxis' and 'tenofovir' to identify literature on PrEP safety trials and issues. The coverage dates were from January 2001 to April 2016. We limited the search to articles in English, which were completed with results available and based on the safety or efficacy of TDF, FTC and TDF/FTC. We profiled our findings on safety concerns of PrEP. Information on clinical trials was extracted from PubMed, Aids Vaccine Advocacy Coalition and clinical-trials.gov based on completed studies (Fig. 1).

In the clinical trials database, studies that were enrolling or incomplete at the time of this review were excluded. Seventy-two cases were retrieved. We modified the search for closed

and completed studies and reduced the number to 42. Further modification with emphasis on the drugs of interest reduced the trials to 23. We then isolated nine studies that were complete with results and enough data for our review (Fig. 1).

In PubMed, we obtained 938 articles after the initial search. We then limited the search to only clinical trials and obtained 79. We then modified to include only trials involving TDF/FTC and TDF and got 35 articles. From here, we isolated 29 articles that were completed and had results. We then focused on efficacy and safety, and retrieved nine articles.

For AVAC, the initial search on PrEP and then clinical trials and product development yielded 38 articles; we then selected completed studies and obtained 14 articles. We then modified to focus on efficacy and safety and isolated eight articles. We then isolated 11 studies that appeared in all three search engines that satisfied our review requirements and used these for our review and discussion (Fig. 1).

RESULTS

Clinical Trials Supporting the Use of PrEP

Numerous trials involving both humans and animals have tested oral and vaginal routes of administration of PrEP and have been found efficacious in preventing HIV. The basis for PrEP stems from results of clinical and epidemiological research [22–25]. We reviewed 11 clinical trials on PrEP among different risk groups conducted from 2005 to 2015. These trials had results at the time of our study and allowed for review. Results from literature on PrEP studies are not necessarily universal. The efficacy ranges from lack of protection to protection levels of as high as 96%, attesting to the complex nature of PrEP implementation [26]. Aside from the effectiveness of PrEP in most of the studies cited, the Vaginal and Oral Interventions to Control the Epidemic (VOICE) [27] and Preexposure Prophylaxis Trial for HIV Prevention among African Women (FEM-PrEP) [28] studies were terminated ahead of time because the analysis failed to demonstrate efficacy attributed to poor adherence. Results for the VOICE study differ with findings in three other placebo-controlled vaginal PrEP trials [Partners PrEP [14], TDF2 [17], Iniciativa Profilaxis Pre-Exposicion (iPrEx) and [16] one placebo-controlled vaginal gel trial [Centre for AIDS program of Research in South Africa (CAPRISA 004)] [18]. Partners PrEP [14] studied Truvada and TDF alone in HIV-discordant committed African couples, TDF2 [17] studied heterosexual African women and men, iPrEx [16] studied gay and bisexual men on four continents and CAPRISA 004 [18] studied South African women. Poor adherence as in FEM-PrEP was the main reason for failure in all three VOICE arms. Among 334 women who became infected with HIV, 22 entered the trial with acute HIV infection. With their exclusion, HIV incidence was 5.7 per 100 person-years, meaning about 6 in every 100 women got infected in every 12 months. HIV incidence rates per 100 person-years were 6.3 and 4.2 for oral TDF vs. placebo, 4.7 and 4.6 for Truvada vs. placebo, and 5.9 and 6.8 for TDF gel vs. placebo; therefore, none of the three strategies worked as hazard ratios (HRs) was for oral TDF: HR 1.49 [95% confidence interval (CI) 0.97–2.29], oral Truvada: HR 1.04 (95% CI 0.73–1.49) and TDF gel: HR 0.85 (95% CI 0.6–1.2). In all cases, women reported 90–91% adherence

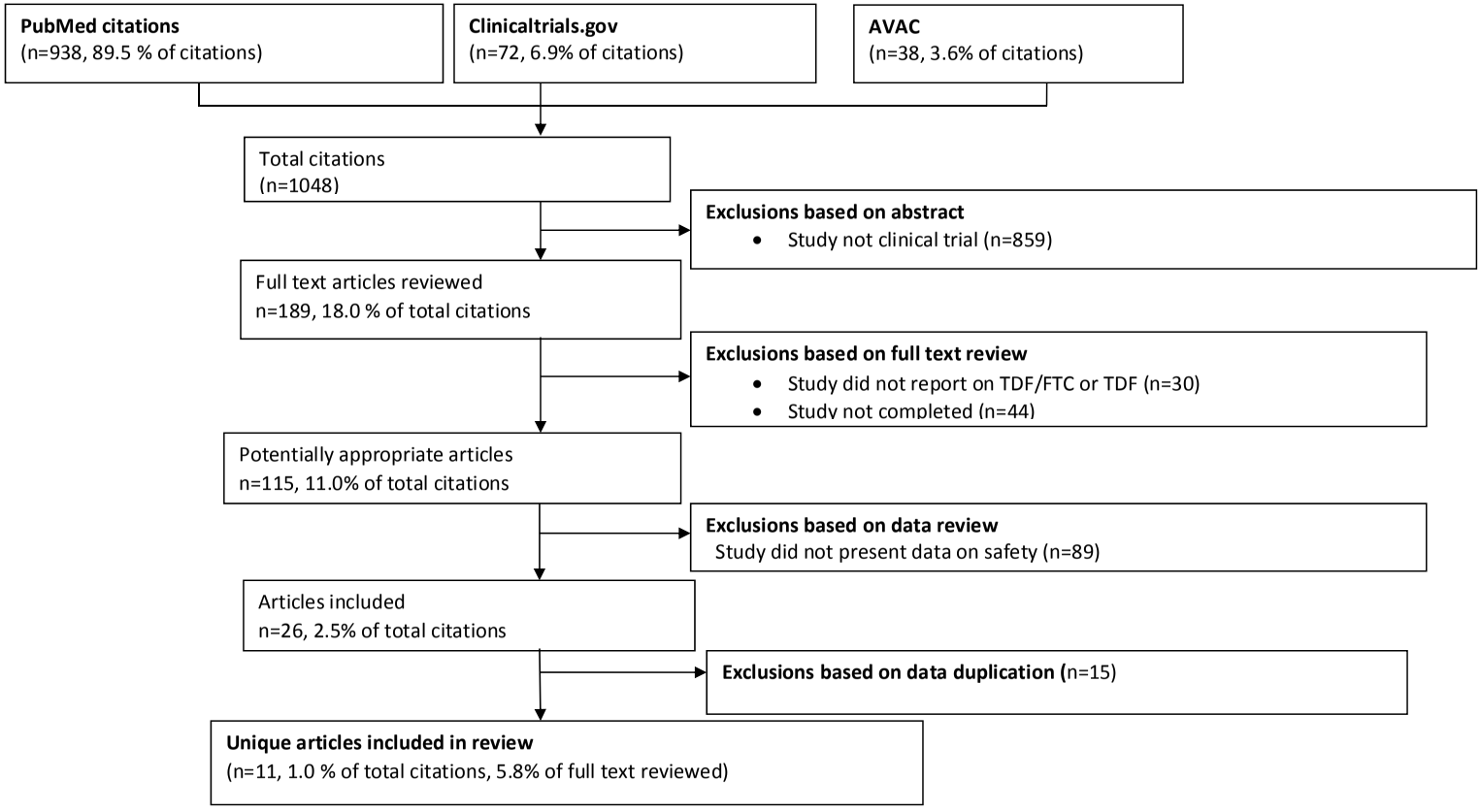

Figure 1. Chart of search strategy for clinical trials on PrEP based on tenofovir (TDF), emtricitabine (FTC) and TDF/FTC combination. AVAC Aids Vaccine Advocacy Coalition

with return data suggesting the same, but TDF concentrations in plasma told another story: 30% or fewer women in all three treatment arms had detectable concentrations in plasma: 30% in oral TDF, 29% in oral Truvada and 25% using TDF gel. In all three again, 50% or more women never had detectable blood in any sample. Three factors predicted detectable TDF in plasma: first, being married (adjusted odds ratio = 2.24 [95% CI, 1.12–4.49]), the second being older than 25 years (adjusted odds ratio = 1.62 [95% CI, 1.12–2.34]), and the third being multiparous (adjusted odds ratio = 1.84 [95% CI, 1.26–2.69]).

The FEM-PrEP [28] study of 2120 participants reported 56 new HIV infections 14 months after initiation of the study with the infections equally distributed between Truvada and placebo groups (28 in each arm), clearly indicating the lack of protection in the use of Truvada. Overall adherence (based on participants self-report) was 95% with no clear difference in adherence between the two arms.

These two results revealed that "products that are long acting and require minimum daily adherence may be more suitable for the population under study" contrary to positive results posted by the other findings, which suggest that young, sexually active, single people can be motivated to take oral Truvada or TDF gel regularly enough to protect themselves from HIV. However, the CAPRISA 004 trial [18] differed from the FEM-PrEP [28] and VOICE [27] studies by determining a 65% protection against HIV at a TDF concentration of [100 ng/mL and up to 76% with a TDF concentration of [1000 ng/mL. Results from Pre-exposure Prophylaxis to Prevent the Acquisition of HIV-1 Infection (PROUD) [29] in the UK and Intervention Preventive de l'Exposition aux Risques avec Risques avec et pour les Gays (Ipergay) [5] in France both showed that PrEP reduced infections among gay men by 86%. None of the participants on PrEP involved in these studies acquired HIV. PrEP was also found to be effective for heterosexual men and women: a study in East Africa (Partners) [14] reduced possible HIV infection within couples in which one partner was positive by 75%. The iPrEx study also found that the HIV infection rate in HIV-negative gay men who were given a daily pill containing Truvada was reduced by 44%, compared with men given placebo. Those who confirmed adherence at 90% had a reduction rate of up to 73%. The TDF2 trial in Botswana gave a reduction rate of 63% against placebo and 77.9% after secondary analysis; therefore, confirming the obvious benefit in the use of PrEP. The Bangkok Tenofovir Study [30] focused on men and women who inject drugs and found that the risk of acquiring HIV reduced by 49% and up to 79% in those who adhered consistently to their medication. The study also found that participants taking TDF were more likely to experience nausea and or/vomiting than those in the placebo group. No indication of elevated creatinine or renal impairment in the TDF group was reported.

The PrEP study in USA with 373 participants with 186 taking TDF and 187 taking placebo was successful with only four on placebo and three among the delayed-arm participants sero-converting [31]. Estimated adherence by pill load was 92% and by medication event monitoring system was 77%. Oral TDF was well tolerated with no significant renal concerns, while adverse drug events reported did not differ significantly between TDF and placebo arms.

Sensitivity analysis on oral PrEP demonstrated that both TDF/FTC and TDF are efficacious in the prevention of HIV infection for a variety of high-risk populations irrespective of country [32, 33]. Both daily and intermittent dosing of PrEP has proven effective and safe [15]. Pharmacokinetic modelling of the pre-exposure prophylaxis initiative (iPrEx) data revealed that a PrEP dose regimen of 7 days in the week dosing could achieve as high as 99% efficacy in the prevention of HIV infection among MSM. Additionally, an intermittent dosing of 4 days in the week could result in 96% efficacy [15]. In a laboratory analysis, detectable blood concentrations of medications used for PrEP were consistently associated with a protective effect against HIV acquisition [16].

Safety Concerns

Adverse reactions to medications used for any intervention are undoubtedly a primary safety concern irrespective of the duration of use. A qualitative study of gay and bisexual sero-discordant male couples assessed the concerns for adoption of PrEP and revealed that the main concerns and probable barriers to adoption of PrEP were short- and long-term side effects or adverse effects due to intermittent dosing or early termination of drug use aside from cost and accessibility of the drugs [34]. In this review, we acknowledge that the trials discussed are short term and do not give the opportunity to assess the long-term, real-world safety profile of the products used for PrEP. Pre-exposure prophylaxis is premised on ARV medications that have been used by people living with HIV and AIDS for quite some time now, since the inception of ARVs. We would expect based on current evidence that the long-term safety profile will be within acceptable limits with favourable benefit-risk profiles, considering the impact of PrEP on HIV prevention. Nonetheless, established adverse drug events such as renal impairment, reduction in BMD, and gastrointestinal (GI) disturbances captured in scientific literature concerning the use of TDF should be considered and monitoring is recommended in PrEP use. An earlier study by the same authors on the association between the occurrence of adverse drug events and the modification of first-line highly active antiretroviral therapy in Ghanaian patients established that adverse drug events play a major role in treatment modification and could be used as a predictor for possible therapy modification [35].

Other concerns on the use and implementation of PrEP include resistance to PrEP medications, feasibility, acceptability and very importantly adherence to PrEP regimens. Because of the importance of PrEP in reducing the spread of HIV, it is critical that these concerns are addressed and fears alleviated to allow for the promising potential of PrEP. The US Public Health Service recommended guidelines for the use of PrEP in 2014 [21] and the CDC has interim guidelines for clinicians on the use of PrEP [36]. Essential factors to be considered before using PrEP include a confirmed HIV-negative status with a normal renal function and a negative hepatitis B status [19, 20]. Recipients of PrEP should be at high risk for HIV infection, receive behavioural and adherence counselling, and need to be tested on a minimum of a quarterly basis during follow-up to ensure they remain HIV negative [21, 36].

Adverse Effects

The TDF/FTC (Truvada) combination or TDF alone used for PrEP generally shows a tolerable profile. In most studies, the experienced side effects did not differ significantly from rates among participants taking placebo. The side effects or adverse events are basically of GIT origin and more prevalent at the start of use, but subside within a month of use. The GIT disturbances are generally upset abdominal pain, nausea, vomiting or diarrhoea. Other reported adverse events not of GIT origin are dizziness, headache, fatigue, weight loss, shortness of breath, cough, anxiety, fever or joint and muscle pain. In most studies, these side effects or adverse events did not differ significantly from rates among participants taking placebo.

Risk factors in long-term use include age, duration of treatment with TDF, elevated baseline creatinine levels, and treatment with a protease inhibitor boosted with ritonavir combinations and among persons with African descent as against Caucasians [37]. Side effects considered potentially serious in the daily use of Truvada or TDF for PrEP are liver function problems, kidney damage, hypophosphatemia, proteinaemia or glucosuria, pancreatitis, bone thinning and lactic acidosis. Flu-like symptoms, hypertriglyceridemia, increased creatinine phosphokinase, unusual dreams and hyperpigmentation are associated with the use of FTC. The Partners PrEP safety trial [14], the iPrEx [16] and the Bangkok Tenofovir studies [30] all recorded increased serum creatinine levels but analyses indicated that they were statistically insignificant compared with placebo. However, changes in estimated glomerular filtration rate were associated with a small but statistically significant decline in the estimated glomerular filtration rate, which was non-progressive and resolved with TDF discontinuation. The use of TDF alone is also associated with liver and pancreatic problems as well as depression [38]. The iPrEx study found a modest effect on BMD reduction in men who participated in the study. The study compared changes in BMD between placebo group and study participants with blood concentrations of tenofovir diphosphate associated with 90% efficacy and use of two to three tablets per week. There was a decline of 1% in the hip and 1.8% in the spine by the end of the study in those with optimal TDF diphosphate concentrations but this reduced to normal levels after 1.5 years of stopping PrEP [16]. The loss of BMD could lead to potential bone fractures and is a problem for TDF-based PrEP. This could be because of phosphate wasting. TDF/FTC was well tolerated with some nausea but little difference was observed between participants and those taking placebo (9 vs. 5%). No differences in severe (grade 3) or life-threatening (grade 4) adverse laboratory events were observed between the active and placebo groups [8].

In the CAPRISA 004 study [18], hepatic flare (defined as an event with an abrupt rise of alanine aminotransferase levels to more than five times the upper limit of normal) during chronic hepatitis B virus infection and considered to be the result of a human leukocyte antigen-1 restricted, cytotoxic T lymphocyte-mediated immune response against hepatitis B virus [39] was observed for two hepatitis B carriers but this did not result in drug discontinuation. In the Partners-PrEP study [14], there were no significant differences across

the study arms with respect to serious adverse effects including the total of 1% deaths per arm.

The US MSM safety trial [31] presented no marked difference in the overall frequency of adverse events between TDF and placebo groups, but in a subset of men at a San Francisco site (n = 184), the use of TDF was associated with a small but statistically significant decrease in BMD at the femoral neck (1.1%) and total hip (0.8% decrease) but no bone fractures were detected. Rates of nausea and vomiting were higher among the TDF than among placebo recipients in the first 2 months in the Bangkok Tenofovir Study [30] but not thereafter. The rates of adverse drug events, deaths or elevated creatinine were not different between the TDF and the placebo groups [30].

Concerning the trials with questionable efficacy, the FEM-PrEP trial [28] presented adverse drug events of nausea and vomiting, which were transient, and a mild elevation of liver enzymes was much more common with the TDF/FTC group than that of placebo group. No change in renal function was reported in either group. In the VOICE study [27], a confirmed increase in creatinine levels was observed in the oral TDF/FTC group than in the oral placebo group. There were no significant differences between the active products and placebo groups for other safety outcomes [27].

Resistance

Generally, resistance to PrEP is rarely observed in sero-converters who are infected with HIV after randomisation. Participants who show resistance are more likely to be the result of circulating resistance and not necessarily, PrEP induced. In the PROUD trial, no one acquired resistance to TDF [29]. Resistant virus reported in studies include one with TDF-resistant virus (K65R mutation) in a participant randomised to TDF and one with FTC-resistant virus (M184V mutation) in a participant randomised to FTC/ TDF from the Partners-PrEP trial [14]. They were found to be infected at randomisation. A rare TDF resistance mutation (K65N) was however reported in the TDF arm of the Partners-PrEP study after randomisation [14]. In the TDF2 study, K65R, M184V and A62V resistance mutations occurred in one participant in the TDF/FTC group. The participant was later found to have had HIV infection at enrolment. The iPrEx study presented two of two men in the active group and one of eight in the placebo group with FTC-resistant virus. TDF/FTC resistant virus was detected in five women (one in the placebo group and four in the TDF/FTC group) in the FEM-PrEP study [28]. Two women from the TDF/FTC group who were determined after enrolment to have had acute HIV infection at baseline had the virus with the M1841/V mutation associated with FTC resistance. One other woman also had the M1841/V mutation but acquired the HIV infection after enrolment. The development of a resistant mutation seems to be more common with FTC than TDF. Additional care must be deployed to ensure that PrEP use is not approved during the acute infection stage to prevent the development of resistance strains. An abstract authored by Knox et al. presented at the CROI 2016 conference in Boston, MA, USA titled "HIV-1 infection with multiclass resistance despite PrEP" provided evidence of

breakthrough HIV infection irrespective of long-term adherence to FTC/TDF (monitored via clinical and pharmacokinetic data) and described a resistant strain irrespective of long-term adherence [40]. It is described as the first such report and more efforts would be deployed to closely monitor the use of PrEP following this report.

The other area of concern is sexual and reproductive health because women of childbearing age are prone to HIV infection and the use of PrEP in discordant relation-ships could be useful. The Partners PrEP and the FEM-PrEP studies showed that TDF based PrEP does not affect the effectiveness of hormonal contraception and neither does hormonal contraception affect PrEP efficacy [14, 28]. There were not significant differences in pregnancy related and infant adverse reaction including premature births, congenital anomalies and growth throughout the early years of life for infants born to women who received PrEP as against placebo in the Partners PrEP study. Therefore, PrEP is relatively safe to be used by women of child-bearing age [14] though, like all medicines, its benefits should be weighed against any risks that it may pose in specific individuals.

Feasibility and Acceptability

Some research on behavioural tendencies has helped to determine adherence to PrEP, but few studies have assessed the acceptability and use of PrEP. Factors associated with intentions to use PrEP in a sample of men who have sex with men (MSM) in USA included the efficacy, costs and potential side effects of PrEP [41]. Preliminary findings from the PrEP Safety trial showed that MSM attending the STD clinic in San Francisco had a high interest in taking PrEP. This trial also demonstrated feasibility of including PrEP in busy clinical settings, indicating that PrEP can be accessed at clinics providing HIV care management [42]. Project PrEP, a study on the acceptability and feasibility of PrEP among young men who have sex with men, reported of high feasibility and acceptability of PrEP [43]. The PROUD study also affirmed the feasibility of incorporating PrEP in routine activities of clinical set-tings [29]. Acceptability of PrEP as demonstrated in a study among MSM and female sex workers in Nairobi and Mtwapa, Kenya, was also rated as high [44]. Suggestions proposed in this study included how best to improve the pill characteristics to make it easy to take, how to reduce stigma and discrimination from other family members, certain barriers and facilitators to adhering to PrEP regimens such as lifestyles, dosing regimen and side effects were identified. Enhanced counselling and commitment to using the products also improved their ability to adhere to the regimens despite the challenges.

Participants in all the listed studies were receptive to monthly HIV testing and counselling, risk reduction counselling, physical examinations and group-based intervention sessions. Participants were more likely to accept a daily pill compared with multiple daily pills administration, especially if they knew their partner was not infected [43]. The Ipergay trial demonstrated that high-risk MSM who do not use condoms consistently, accepted on demand PrEP as a practical alternative to daily PrEP if its effective [5]. A sub-study of The Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking [45] study involving

37 men in Harlem revealed scepticism and distrust by male partners and sometimes resulted in unwillingness of partners to engage in sex after learning about their PrEP use, thus pointing out how stigma and social barriers may impede adherence and therefore acceptability.

Adherence

Six clinical trials yielded PrEP efficacy estimates of 0–75% mostly because of differences in adherence among the studies [14, 16, 17]. Self-reported adherence to PrEP is unreliable as the initial clinical trials quickly established that blood drug concentrations sharply differ from perceived adherence claims. Effective counselling and other support measures are required in all persons who desire to use PrEP for HIV prevention.

The iPrEx study [16] clearly illustrated how adherence produced different outcomes in HIV-negative gay men who were given a daily pill of TDF and FDC and achieved a reduction rate of 44% as against men given a placebo. It was realised that subjects who by self-report and pill count took the drugs more than 90% of the time reduced the infection rate by 73% [16]. Meanwhile, another interesting finding of the trial indicated that while 93% of trial subjects reported complete compliance, only 51% actually com-plied effectively when drug concentrations in blood were determined [16]. The investigators concluded through calculations that a reduction in the risk of HIV infection could have been as much as 92% compared with placebo if the study subjects had complied totally [16]. This confirms the importance of adherence as a major tool to be deployed in PrEP. The FEM-PrEP trial [28], which was halted for futility, reported adherence by self-report and pill count as high, but plasma drug concentrations showed that only 15–26% of samples from HIV seroconverters had detectable concentrations of serum TDF and only 26–38% of non-seroconverting controls. This low level of adherence was recorded as 37% (Table 1) by the researchers and this may have resulted in the inability to assess the protective effect of Truvada in FEM-PrEP trial. This again points to the importance of ensuring adherence in PrEP management.

Liu et al. [42], examined self-reported medication-taking experiences, facilitators and barriers of medication adherence among a geographically diverse online sample of HIV-uninfected MSM in US. Their multivariable analyses showed that age and sex were likely associated with adherence. In this study, 1480 men having sex with other men were surveyed, 806 (54%) of participants indicated regular taking of medicines, 80% of this number reported taking medicines for treatment whilst 55% said they take medicines for preventive purposes. The study also realised that men aged older than 25 years were more likely to report excellent adherence together with those who did not report any adherence barriers. Willingness to use PrEP was also associated with high likelihood of reporting perfect 30-day adherence. They listed factors that improved medication adherence as establishing a routine, keeping medication visible and using a pill-box. Forgetfulness, changes in usual routine, and being busy or away from home were listed as barriers to adherence [42]. Counselling strategies to build pill-taking routines can help improve adherence to PrEP. Daily dosing is much more associated with a high level of adherence than post-coital use of PrEP, which is generally low [15].

Following the approval of the use of PrEP in USA and Europe, reports on adherence have been claimed to be higher in recent trials and open label extensions as compared with the initial clinical trials. Explanations provided include available evidence of PrEP efficacy and individual motivations and reasons for taking PrEP [46].

DISCUSSION

The advent of PrEP is a promising turning point in the prevention of HIV among at-risk groups. TDF-based PrEP is recommended to prevent HIV infection in tandem with other preventive measures. From the trials reviewed, it is evident that PrEP is highly effective against HIV infection when taken as required. Most importantly, PrEP seems to be characterised by low adverse effects. Our current review shows a favourable pattern of adverse events for PrEP among eligible populations. Side effects can lead to a lack of compliance, resulting in low levels of adherence (frequency of medicine intake) to pill use. Some reported symptoms associated with the start of PrEP gradually resolve. Generally, even for some side effects listed as serious, such as kidney dysfunction, observed increases in the serum creatinine level return to normal after the discontinuation of PrEP. Tubular renal toxicity from PrEP is rare and active screening is not recommended. The same applies to the reduction of BMD after cessation in the use of TDF and therefore current evidence does not support constant X-ray monitoring at baseline before initiating PrEP and while taking TDF/FTC.

Liver toxicity mentioned earlier in the findings was reported by the D.A.D. study, which looked at the use of antiretroviral therapy and the risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons. It concluded among that alongside other antiretroviral agents, TDF is associated with an increased risk of end-stage liver disease among HIV-positive patients on long-term therapy. It also indicated that the unexpected viral hepatitis independent TDF association should be investigated further [47]. The use of TDF-based PrEP is yet to present any case report involving serious hepatic complications. However, the regular monitoring of liver enzymes in PrEP uses would be helpful in preventing possible toxicities.

The correspondent decrease in sexual risk behaviour among participants in the course of PrEP is very encouraging. This is attributed to behavioural intervention including sexual health counselling and the provision of condoms across the studies where applicable. Undoubtedly, behavioural interventions should be an integral part of PrEP.

Because PrEP is meant for HIV-negative individuals, an important aspect of PrEP is the identification of people who are seroconverting [14]. Preliminary testing methods, for example polymerase chain reaction that can diagnose people who are recently infected with HIV, are thus important but expensive. This will enable provision of treatment options instead of preventive interventions.

Exclusion criteria that run across trials were the low level of creatinine clearance below 50 mL/min, some cases of hepatitis and evidence of bone fractures. People who do not qualify for PrEP but are at risk for HIV should be encouraged to adhere to good evidence-

Table 1. Abstract on Clinical Trials on Pre-Exposure Prophylactic Agents (Tenofovir and Emtricitabine)

Study	Study Design	Study population	Sample size
iPrEx Trial [16]	Placebo controlled RCT	MSM	2499
TDF2 [17]	Placebo controlled RCT	Heterosexual adults	1219
Partners PrEP [14]	Placebo controlled RCT	Heterosexual couples	1013
VOICE [27]	Placebo controlled RCT	Women of reproductive age	3019
FEM-PrEP [28]	Placebo controlled RCT	High risk women	2120
PROUD [29]	Placebo controlled RCT	MSM	545
Ipergay [5]	Placebo controlled RCT	MSM	400
ADAPT [44]	Placebo controlled RCT	MSM; TGW	179
The Bangkook Tenofovir study [30]	Placebo controlled RCT	Drug injectors	2413
CAPRISA 004 Trial [18]	Placebo controlled RCT	Women of reproductive age	889
PrEP safety trial [31]	Placebo controlled RCT	MSM	400

NR=Not reported; MSM=Men who have sex with men; TDF=Tenofovir; FTC= Emtricitabine; MEMS=Medication event monitorin
Centre for AIDS program of Research in South Africa; FEM PrEP=Prexeposure Prophylaxis Trial for HIV Prevention among Af
Exposure Prophylaxis Pill Taking; PROUD= Pre-Exposure prophylaxis to prevent the acquisition of HIV-1 infection; IperGAY= In

based sexual behavioural prevention practices including regular condom use. The reduction in rates of sex without condoms from 27 to 9% after 24 months of the Partners-PrEP trial [14] is encouraging and shows that counselling and education on good sexual practices is complementary on HIV prevention. Several other studies [48–51], including studies con-

	Agent used	Objective	Outcome/Results
	TDF/FTC	Effectiveness	44%
		Safety	Nausea; ↑serum creatinine
		Adherence	51%
	TDF/FTC	Effectiveness	62%
		Safety	Dizzines; Nausea; Vomitting; ↓bone mineral density
		Adherence	84%
	TDF vs TDF/FTC	Effectiveness	67% (TDF); 75% (TDF/FTC)
		Safety	GIT; Fatigue; Neutropaenia; ↑serum creatinine; ↓phosphorous
		Adherence	82%
	TDF vs TDF/FTC	Effectiveness	-49% (TDF); -4% (TDF/FTC)
		Safety	↑serum creatinine
		Adherence	28-29%
	TDF/FTC	Effectiveness	6%
		Safety	Nausea; Vomiting; ↑ALT; Hepatic and renal abnormalities
		Adherence	37%
	TDF/FTC	Effectiveness	86%
		Safety	Nausea; Diarrhoea; Abdominal pains; Fatigue; Headache; Flu-like illness; Sleep disturbance; ↑creatinine clearance
		Adherence	86%
	TDF/FTC	Effectiveness	86%
		Safety	Abdominal pains; Nausea; Vomiting; Diarrhoea
		Adherence	43% optimal use; 25% suboptimal use by ACASI
	TDF/FTC	Effectiveness	NR
		Safety	Nausea; Unintentional weight loss; ↑serum creatinine
		Adherence	Daily-79%; Time driven-63%; Event driven-53%
	TDF	Effectiveness	48.9%
		Safety	Nausea; Vomiting
		Adherence	83.8%
	TDF	Effectiveness	39%
		Safety	↑serum creatinine; Anaemia; Diarrhoea
		Adherence	NR
	TDF	Effectiveness	NR
		Safety	Back pain; ↓ in bone mass density; Hypophosphatemia
		Adherence	92% (pill count); 77% (MEMS)

g sysytem; RCT=randomised controlled trial; TGW=Trans-gender women ; iPrEX=Iniciativa Profilaxis Pre-Exposicion; CAPRISA= rican Women; VOICE= Vaginal and Oral Interventions to Control the Epidermic; ADAPT=Alternative Dosing to Augment Pre- ntervention Preventive de l'Exposition aux Risques avec Risques avec et pour les Gays;PrEP =Pre-exposure prophylaxis

ducted in West African women with TDF, also demonstrate a reduction in high-risk sexual behaviour with counselling during PrEP [52]. TDF/FTC is the only medication with a label indication as PrEP against HIV infection, but new PrEP drugs and formulations are being considered for future trials (Maraviroc, intravaginal rings containing dapivirine and TDF) and

long-acting injectables (rilpivirine, carbotegravir). These newer agents also present a good safety profile when used for the treatment of HIV infection, but use for PrEP purposes in HIV-uninfected persons is unknown as efficacy and clinical safety is yet to be established [37]. A new formulation, tenofovir alafenamide that provides 90% lower plasma levels of TDF concentrations compared with standard TDF, has recently being approved by the FDA. It is claimed to have favourable renal and bone safety profile better than original TDF, unfortunately as at the time of this review efficacy and safety in PrEP has not been established in HIV-negative populations [37].

CONCLUSION

The medications currently studied for PrEP (TDF and FTC) are efficacious and seem to have a good safety profile within the average short period of 3 years studied. Emphasis on the use of additional prevention methods should be made alongside. The main adverse effects observed with PrEP are GI related and graded below 2 for severity. These are basically mild to moderate nausea, vomiting and diarrhoea. Major concerns are renal, hepatic and bone toxicity, but these are transient and non-progressive and quickly resolved after discontinuation of TDF. Overall, the benefit-risk profiles of the products used for PrEP appear favourable.

PrEP as an intervention to reduce HIV transmission appears to have a safe benefit-risk profile in clinical trials. It is recommended for widespread use but adherence monitoring and real-world safety surveillance are critical in the post-marketing phase to ensure that the benefits observed in clinical trials are maintained in real-world use. Behavioural counselling and assurance of safety and efficacy are important components of PrEP. Other factors of PrEP implementation that have been suggested include improving access, averting stigma, cost effectiveness, and education on PrEP to improve knowledge and assure people of the efficacy profile of products used for PrEP. Further studies must ultimately look at how safe and beneficial PrEP could be for pregnant women and women seeking to get pregnant.

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Chapter 3

PHARMACOVIGILANCE OF ANTI-RETROVIRAL THERAPY

Chapter 3.1

ASSOCIATION BETWEEN THE OCCURRENCE OF ADVERSE DRUG EVENTS AND MODIFICATION OF FIRST-LINE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN GHANAIAN HIV PATIENTS

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ABSTRACT

Introduction

Patients initiated on highly active antiretroviral therapy (HAART) generally remain on medication indefinitely. A modification in the HAART regimen may become necessary because of possible acute or chronic toxicities, concomitant clinical conditions, development of virological failure or the advent of adverse drug events. The study documents adverse drug events of HIV-positive Ghanaian patients with HAART modifications. It also investigates the association between documented adverse drug events and HAART modification using an unmatched case–control study design.

Method

The study was conducted in the Fevers Unit of the Korle Bu Teaching Hospital and involved patients who attended the HIV Care Clinic between January 2004 and December 2009. Data from 298 modified therapy patients (cases) were compared with 298 continuing therapy patients (controls) who had been on treatment for at least 1 month before the end of study. Controls were sampled from the same database of a cohort of HIV-positive patients on HAART, at the time a case occurred, in terms of treatment initiation ±1 month. Data were obtained from patients' clinical folders and the HIV clinic database linked to the pharmacy database. The nature of the documented adverse drug events of the cases was described and the association between the documented adverse drug events and HAART modification was determined by logistic regression with reported odds ratios (ORs) and their 95 % confidence interval (CI).

Results

Among the 298 modified therapy patients sampled in this study, 52.7 % of them had at least one documented adverse drug event. The most documented adverse drug event was anaemia, recorded in 18.5 % of modified therapy patients, all of whom were on a zidovudine-based regimen. The presence of documented adverse drug events was significantly associated with HAART modification [adjusted OR = 2.71 (95 % CI 2.11–3.48), $p < 0.001$].

Conclusion

Among HIV patients on HAART, adverse drug events play a major role in treatment modification. Occurrence of adverse drug events may be used as a predictor for possible therapy modification. We recommend the institution of active pharmacovigilance in HIV treatment programmes as it permits the proper identification and characterisation of drug-related adverse events. This can help develop approaches towards their management and also justify therapy modifications.

INTRODUCTION

Patients started on highly active antiretroviral therapy (HAART) generally remain on medication indefinitely. The World Health Organization (WHO) recommends first-line regimens involving two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral (ARV) drug [1, 2]. Second-line regimens are started when the first-line regimens are ineffective. The provision of second-line regimens in resource-limited settings is generally a challenge [3, 4].

Therapy modifications in ARV regimens become necessary because of possible acute or chronic toxicities, concomitant clinical conditions, development of virological failure or the advent of adverse drug events. Drug substitution is defined as the replacement of one or more drugs in the first-line ARV regimen (NRTI or NNRTI) with another drug from the same ARV class (NRTI or NNRTI), e.g. the substitution of nevirapine (NVP) with efavirenz (EFV) or the substitution of an NRTI, stavudine (d4T), with zidovudine (ZDV). Therapy switch on the other hand refers to the change from the first-line NNRTI-based HAART to a second-line protease inhibitor-based ARV regimen [1, 5].

A major constraint of HAART is the high prevalence of adverse drug events among patients receiving HAART. Adverse drug events are a very common complication of ARV therapy and a major reason for patients defaulting during HIV therapy [6]. The incidence is high in the initial stages, but tends to decrease later, though long-term events such as lipodystrophy may occur [7, 8]. Up to 25 % of patients discontinue their initial HAART regimen because of treatment failure, toxic effects or non-adherence within the first 12 months of therapy [6, 9]. This poses a huge challenge in the fight against HIV. While research for less toxic ARVs continue, it is important to monitor treatment-associated toxicities with a view to understanding and managing them where possible.

The approach to patients who need HAART modification depends on several factors. These include the reason for change, previous HAART experience, available treatment options and the tolerability of the HAART. In addition, adverse drug events associated with some ARVs (e.g. lipodystrophy, anaemia, renal impairment) further limit the type of ARVs that can be administered to patients [10, 11]. Adverse drug events, if not managed effectively, will lead to medication non-adherence and invariably to treatment failure [10, 11].

In Ghana, the Korle Bu Teaching Hospital (KBTH) has been providing HAART services to patients living with HIV/AIDs (PLWHA) since 2003 at a token fee of US $3.00 in response to the WHO "3 by 5" initiative for all nations, with the objective of placing 3 million persons living with HIV on HAART by 2005 [12]. As at 2015, about 11,000 people living with HIV/AIDS were on HAART in the KBTH, with some on treatment for the past 11 years. No singular effort has been made to analyse the factors associated with HAART modification from the data generated so far. There is also limited local data on the profile of adverse drug events. Determining the various factors associated with HAART modification and profiling the adverse drug events in patients on ARVs is an important step to the success of any HAART programme.

The study was in two parts; the first part describes all adverse drug events documented at most 12 months prior to therapy modification in HIV-positive patients who modified HAART at the KBTH in Accra, Ghana, and the second part determines the association between the presence of adverse drug events as a primary exposure and HAART modification as the outcome.

METHODS

Setting

This study was conducted in the Fevers Unit of the KBTH, the premier teaching hospital in Ghana. As of December 2009, about 4850 patients have been initiated on HAART, with about 3440 of them still on treatment. There are three major outpatient clinic days per week, each with an average attendance of 120 patients. As at the time of study, the total number of therapy modifications was about 400 cases. Patients included in the study attended the HIV Care Clinic between January 2004 and December 2009. The HIV clinic runs an electronic database, which served as the source of data. The first-line HAART guidelines in place during the study period were d4T/lamivudine (3TC)/NVP or d4T/3TC/EFV or ZDV/3TC/NVP or ZDV/3TC/EFV, i.e. d4T/3TC/NVP or d4T/3TC/EFV or ZDV/3TC/NVP or ZDV/3TC/EFV. HAART classification as first line or second line was based on the recommendations of the "Guidelines for Antiretroviral Therapy in Ghana" [5]. Regimens in this study are either d4T-based regimens or ZDV-based regimens depending on the type of NRTI involved.

Study Design and Patient Population

This is an unmatched case–control study using data documented in patients' clinical folders during previous hospital visits. The study used data from 298 modified therapy patients (cases) and 298 continuing therapy patients (controls) who had been on HAART between January 2004 and December 2009 and had been on treatment at least 1 month before the end of study. Only patients 15 years or older who were enrolled at the Fevers Unit of the KBTH, were on triple therapy and had available clinical and pharmacy records were included in the study. Cases were defined as patients aged 15 years or older who were on modified HAART (modified therapy patients). Changes in dose were not considered as modified therapy. Controls were defined as patients aged 15 years or older who were still on their initiating HAART (continuing therapy patients). Controls were sampled from the same database of a cohort of HIV-positive patients on HAART at the time a case occurred in terms of treatment initiation ±1 month. Given that cases and controls were sampled based on treatment initiation date, every risk pair had a similar period of observation. A sample size of 298 each for cases and controls was determined as described by Strom [13], with the following assumptions: 10 % expected prevalence of adverse drug events in the controls, a minimum odds ratio (OR) of 2.0 to be detected, a type I error of 5 %, a type II error of 20 % (power of 80 %) and a ratio of cases to controls of 1:1.

Data Collection and Definitions

The outcome variable in this study was HAART modification (i.e. patients who modified initiating ARV therapy compared with patients who continued with initiating ARV), whilst the primary exposure of interest was documented adverse drug events at most 12 months prior to end of study. Data were obtained from patients' clinical folders and the HIV clinic database linked to the pharmacy data-base. We extracted documented adverse drug events from the clinical folders of patients as recorded by the attending physician during patients' follow-up post-treatment initiation. The clinical folder was designed by the National AIDS Control Programme (NACP) [5] for the Ghana Health Service in accordance with recommendations from the WHO, and has specific adverse drug event sections to be completed by the attending specialist physician on each patient's clinic visit. All trained HIV care physicians at all HIV care centres nationwide use this specifically designed clinical folder for every HIV-positive patient on each clinic visit. A sub-section of this clinical folder lists the following adverse drug events for the attending physician to look out for or examine on each clinic visit of the patient; anaemia, rash, diarrhoea ([3 days), pancreatitis, hepatotoxicity, pain/numbness/tingling in extremities, blood in urine, lipodystrophy and depression in addition to other adverse drug event(s) noticed [5]. For the purposes of this study, all adverse drug events documented in the clinical folder at most 12 months prior to HAART modification or end of study were used in assessing the presence of adverse drug events. No causality assessment was done on the adverse drug events data retrieved from documented records. We collected data on socio-demographic, clinical, immunological and virological parameters of the study participants, including gender, education at baseline, marital status at baseline, source of funding health care and occupation at baseline. Clinical and immunological baseline data collected prior to initiation of HAART included presence of systemic signs and symptoms, CD4 count, WHO staging and type of HAART regimen administered. All data extraction from the clinical folders and the electronic database was done by a trained specialist clinical pharmacist, the lead author, using a standardised template that was piloted prior to study implementation to maintain uniformity.

Data Analysis

Data were double entered, cleaned and managed using Microsoft Access (Microsoft Corporation, Redmond, Washington, USA) and analysed using Stata 11.0 (College Station, Texas, USA). Data were expressed as frequencies and percentages for categorical variables. Documented adverse drug event data were reviewed and coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 13.1) terminology and grouped by System Organ Class (SOC) Preferred Term (PT) according to therapy type. MedDRA is a clinically validated inter-national medical terminology used by regulatory authorities, and it organises adverse events by SOC divided into high level group terms (HLGTs), high level terms (HLTs), PTs and lowest level terms (LLTs).

Continuous variables were reported as mean ± standard deviation or median with interquartile (IQR) range if not normally distributed. The presence of documented adverse drug events was the primary exposure variable, whilst HAART modification is the outcome variable. Predictors of HAART modification were determined by logistic regression and reported as OR with corresponding 95 % confidence interval (CI). Covariates for the multivariate analysis were selected by the change-in-estimate method such that variables that change the crude estimate of the association between documented adverse drug events and HAART modification by more than 10 % were considered confounders [14, 15]. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

3.1

RESULTS

Study Population

During the study period between January 2004 and December 2009, 400 patients had their HAART modified. The total number of participants in this study was 596. Cases and controls were similar in socio-demographic characteristics: median age 43.0 years (IQR 36–51) in cases versus 43.0 years (IQR 36–52) in controls and a female population of 65.4 % (n = 195) in cases versus 64.4 % (n = 192) in controls (Table 1).

Clinical characteristics of cases and controls are shown in Table 2. The median duration from initiation of therapy to end of study was 344.5 days (IQR 101.5–882.5) for the cases and 374 days (IQR 104.5–898.3) for the controls. At least one adverse drug event was documented in 157 (52.7 %, 95 % CI 46.8–58.5) of the cases and 12 (4.0 %, 95 % CI 2.1–6.9) of the controls.

Description of Documented Adverse Drug Events

A review of the clinical folders of the cases indicated that 157 modified therapy patients (52.7 %) had at least one documented adverse drug event, 13 patients (4.4 %) had two documented adverse drug events and 144 patients (95.6 %) had one documented adverse drug event (Table 3). From Table 3, the most documented adverse drug event was anaemia (SOC red blood cell disorder), reported in 18.5 % (n = 55) of the modified therapy patients. Metabolic and nutritional disorders were documented in 12.4 % (n = 37) of the modified therapy patients, whilst peripheral neuropathy was documented in 8.7 % (n = 26) of the modified therapy patients (Table 3).

Association Between Documented Adverse Drug Events and HAART Modification

The presence of documented adverse drug events was significantly associated with HAART [crude OR = 2.27 (95 % CI 1.89–2.72)] in the univariate analysis (Table 4). Other factors associated with HAART modification in the univariate analysis were WHO HIV staging at HAART initiation, body mass index (BMI) at HAART initiation, presence of systemic signs and symptoms at HAART initiation and CD4 count at HAART initiation. However, when the change-in-estimate method was used to deter-mine potential confounders to the association

Table 1. Socio-demographic baseline characteristics of case and control subjects

Characteristics	Case subjects [n, %][a]	Control subjects [n, %][a]
Age at HAART initiation	N=298	N=298
Median (Interquartile range), years	43 (36-51)	43 (36-52)
Gender	N=298	N=298
Female	195 (65.4)	192 (64.4)
Male	103 (34.6)	106 (35.6)
Marital status	N=293	N=296
Single	63 (21.5)	55 (18.6)
Married/cohabiting	159 (54.3)	160 (54.0)
Divorced/separated/widowed	71 (24.2)	81 (27.4)
Educational status	N=288	N=295
None	42 (14.6)	41 (13.9)
Primary/Junior high school	132 (45.8)	137 (46.4)
Senior high school	87 (30.2)	92 (31.2)
Tertiary	27 (9.4)	25 (8.5)
Employment status	N=284	N=294
Unemployed	32 (11.3)	27 (9.2)
Employed	252 (88.7)	267 (90.8)
Smoking	N=293	N=295
Non-smoker	273 (93.2)	278 (94.2)
Smoker	20 (6.8)	17 (5.8)
Alcohol use	N=293	N=295
Non-drinker	239 (81.6)	241 (81.7)
Drinker	54 (18.4)	54 (18.3)
Source of funding	N=289	N=293
Self	180 (62.3)	203 (69.3)
National health insurance and other sources	109 (37.7)	90 (30.7)

HAART highly active antiretroviral therapy

[a] Data are reported as n (%) unless otherwise stated

between documented adverse drug events and HAART modification, only BMI at HAART initiation changed the crude OR by [10 % and was thus included in the multivariate analysis. After adjusting for this possible confounder, the odds of HAART modification was 2.71 in patients with documented adverse drug events [adjusted OR = 2.71 (95 % CI 2.11–3.48), $p < 0.001$].

Sub-group analysis of the outcome variable indicated significant association between documented adverse drug events and first-line to first-line HAART modification [adjusted OR = 2.88 (95 % CI 2.22–3.74), $p < 0.001$], but no association with first-line to second-line HAART modification [adjusted OR = 2.33 (95 % CI 0.69–7.91), $p = 0.175$].

Table 2. Clinical characteristics of case and control subjects

Characteristics	Case subjects [n, %][a]	Control subjects [n, %][a]
Duration from HAART initiation to end of study	N=298	N=298
Median (Interquartile range), days	344.5 (101.5-882.5)	374 (104.5-898.3)
Documented adverse event	N=298	N=298
Present	157 (52.7)	12 (4.0)
Absent	141 (47.3)	286 (96.0)
WHO HIV stage at HAART initiation	N=293	N=296
Stage I-III	229 (78.2)	251 (84.8)
Stage IV	64 (21.8)	45 (15.2)
BMI at HAART initiation	N=240	N=240
Under weight (<18.00 Kg/m^2)	76 (31.7)	51 (21.3)
Normal weight/ Over-weight/Obese (≥18.00 Kg/m^2)	164 (68.3)	189 (78.7)
Presence of systemic signs and symptoms at HAART initiation	N=294	N=298
Yes	163 (55.4)	128 (43.0)
No	131 (44.6)	170 (57.0)
CD_4 T lymphocytes count at HAART initiation	N=293	N=295
<150 cells/mm^3	203 (69.3)	168 (56.9)
≥150 cells/mm^3	90 (30.7)	127 (43.1)
HAART regimen administered	N=298	N=298
ZDV/3TC/EFV	70 (23.5)	85 (28.5)
ZDV/3TC/NVP	71 (23.8)	76 (25.5)
d4T/3TC/EFV	84 (28.2)	63 (21.1)
d4T/3TC/NVP	60 (20.1)	61 (20.5)
Others	13 (4.4)	13 (4.4)

3TC lamivudine, BMI body mass index, d4T stavudine, EFV efavirenz, HAART highly active antiretroviral therapy, NVP nevirapine, WHO World Health Organization, ZDV zidovudine

[a] Data are reported as n (%) unless otherwise stated

DISCUSSION

Profile of Documented Adverse Drug Events

At least one adverse drug event was documented in 52.7 % (n = 157) of modified therapy patients, as against 4 % (n = 12) of continuing therapy patients. Similar to other findings, anaemia, nutritional and metabolic disorders and peripheral neuropathy were the most documented adverse drug events [11, 16]. The most documented adverse drug event among the entire study population was anaemia (19.6 %, n = 58), mostly from the use of ZDV, but which was totally absent in patients on d4T-based therapy. A cohort study at the same study site cited anaemia as the most documented adverse drug event [11], similar to other studies [16]. Metabolic disturbances and peripheral neuropathy, the next most documented adverse drug events, were documented mostly in the d4T-based therapies,

Table 3. System-organ classification profile of reported adverse events in case and control subjects on different therapeutic regimens

			1st line therapy									
			ZDV/3TC/EFV		ZDV/3TC/NVP		d4T/3TC/EFV		d4T/3TC/NVP		Others	
Adverse event	Total (Cases) N=298 n, %1	Total (Controls) N=298 n, %	Cases N=71 n, %	Controls N=76 n, %	Cases N=70 n, %	Controls N=85 n, %	Cases N=84 n, %	Controls N=63 n, %	Cases N=60 n, %	Controls N=61 n, %	Cases N=13 n, %	Controls N=13 n, %
Red blood cell disorder	55 (18.5)	3(1.0)	31 (44.3)	1 (1.2)	24 (33.8)	2 (2.6)	-	-	-	-	-	-
Metabolic & nutritional disorders	37 (12.4)	1 (0.3)	-	-	-	-	30 (35.7)	1 (1.6)	7 (11.7)	-	-	-
Peripheral neuropathy	26 (8.7)	1 (0.3)	1 (1.4)	-	1 (1.4)	-	18 (21.4)	1 (1.6)	6 (10.0)	-	-	-
Skin disorder	11 (3.7)	2 (0.7)	2 (2.9)	1 (1.2)	5 (7.0)	-	2 (2.4)	-	2 (3.3)	1 (1.6)	-	-
Neuro-psychiatry disorders	9 (3.0)	3 (1.0)	7 (10.0)	1 (1.2)	-	-	1 (1.2)	2 (3.2)	-	-	1 (7.7)	-
Central & peripheral nervous system disorder	6 (2.0)	-	1 (1.4)	-	-	-	1 (1.2)	-	4 (6.7)	-	-	-
Gastro-intestinal	6 (2.0)	2 (0.7)	4 (5.7)	-	1 (1.4)	-	1 (1.2)	2 (3.2)	-	-	-	-
Cardiovascular	4 (1.3)	1 (0.3)	2 (2.9)	1 (1.2)	-	-	1 (1.2)	-	-	-	1 (7.7)	-
Hypersensitivity	4 (1.3)	1 (0.3)	-	-	2 (2.8)	-	1 (1.2)	1 (1.6)	1 (1.7)	-	-	-
Systematic signs & symptoms	4 (1.3)	1 (0.3)	2 (2.9)	-	-	-	2 (2.4)	1 (1.6)	-	-	-	-
Musculo-skeletal	3 (1.0)	-	1 (1.4)	-	-	-	2 (2.4)	-	-	-	-	-
Liver & biliary system disorder	2 (0.7)	-	-	-	-	-	1 (1.2)	-	1 (1.7)	-	-	-
Bone toxicity	1 (0.3)	-	-	-	-	-	-	-	1 (1.7)	-	-	-
Hearing & vestibular disorder	1 (0.3)	-	1 (1.4)	-	-	-	-	-	-	-	-	-

[1]% are column percentages; ZDV=zidovudine; 3TC=lamivudine; EFV=efavirenz; NVP=nevirapine; d4T=stavudine

Table 4. Socio-demographic and clinical factors associated with HAART modification

Characteristic		Crude odds ratio [95% CI]	p-value	Adjusted odds ratio [95% CI][a]	p-value
Age at HAART initiation		1.00 [0.99-1.02]	0.884	-	-
Gender	Male	0.96 [0.68-1.34]	0.797	-	-
	Female	1.00			
Smoking status	Smoker	1.20 [0.62-2.34]	0.596	-	-
	Non-smoker	1.00			
Alcohol use	Drinker	1.01[0.66-1.53]	0.969	-	-
	Non-drinker	1.00			
Documented adverse drug event	Present	2.27 [1.89-2.72]	<0.001	2.71 [2.11-3.48]	<0.001
	Absent	1.00		1.00	
WHO HIV staging at HAART initiation	IV	1.56 [1.02-2.37]	0.039	-	-
	I-III	1.00			
BMI at HAART initiation	Under-weight (< 18.00 Kg/m^2)	1.72 [1.14-2.59]	0.010	1.76 [1.09-2.84]	0.021
	Normal/Over-weight/ Obese (≥ 18.00 Kg/m^2)	1.00		1.00	
Systemic signs and symptoms at HAART initiation	Present	1.65 [1.19-2.29]	0.002	-	-
	Absent	1.00			
CD_4 T lymphocytes count at HAART initiation	<150 cells/mm^3	1.71 [1.22-2.39]	0.002	-	-
	≥150 cells/mm^3	1.00			
HAART regimen administered	ZDV/3TC/NVP	1.13 [0.72-1.78]	0.585	-	-
	d4T/3TC/EFV	1.62 [1.03-2.55]	0.038	-	-
	d4T/3TC/NVP	1.19 [0.74-1.92]	0.465	-	-
	Others	1.21 [0.53-2.79]	0.647	-	-
	ZDV/3TC/EFV	1.00			

but were totally absent in the ZDV-based therapies. Red blood cell disorders, metabolic and nutritional disorders and peripheral neuropathy were the three leading documented events. Among this group, practically all the people who had a documented red blood cell disorder had been given a ZDV combination. ZDV has long been known to cause anaemia, because of its myelosuppressive activity [17–20]. This haematological reaction occurs when ZDV is given in dosages of C1500 mg daily. Lower dosages of ZDV are used in triple combination therapy as first-line to reduce this reaction. Use of other medications that inhibit cytochrome P_{450} may also enhance the side effects of ZDV since they can inhibit its hepatic metabolism [17, 21, 22]. Patients who experienced metabolic and nutritional disorders had been given a d4T combination. The majority of people who experienced peripheral neuropathy were also on d4T, and they reported a greater variety of adverse drug events. These adverse drug events with d4T have been demonstrated in several studies [23–25]. Metabolic and nutritional disorders such as hyperlactataemia, lactic acidosis, lipoatrophy and in some cases hypertriglyceridemia as well as hypercholesterolaemia [26] can lead to several cardiovascular diseases. Ter Hofsted et al. noted that these effects are also more pronounced with higher doses of d4T and recommend plasma monitoring of d4T as a way to prevent d4T-associated lipoatrophy [25].

Studies have shown that the most common adverse effects associated with discontinuation of HAART are gastrointestinal [6]. These commonly include anorexia, nausea, vomiting and diarrhoea. A pharmacovigilance study of adults on HAART in South Africa indicated that out of a total of 2585 patients monitored over a period of 5 years, 34.5 % had their initiation regimens changed and this substitution/switch occurred on average of 14.9 months after HAART initiation [27]. The study also showed that the four most common adverse drug events experienced by the patients who switched therapy due to ARV-related toxicity were polyneuropathy (24.0 %), lipodystrophy (23.9 %), neuropathy (10.6 %) and suspected lactic acidosis (3.8 %). Another study in a South African cohort indicated that the frequency of therapy switch (within 3 years of HAART initiation) due to NVP toxicity is about 8 %, EFV toxicity 2 % and ZDV toxicity 8 % [28]. The study also indicated that therapy switch due to d4T toxicity occurred in 21 % of patients due to symptomatic hyperlactataemia (5 %), lipodystrophy (9 %) or peripheral neuropathy (6 %).

The high proportion of first-line to first-line HAART modification (80.5 %, n = 240) versus first-line to second-line HAART modification (19.5 %, n = 58) among the modified therapy patients participating in this study is similar to that reported in other studies in developed countries [29, 30]. The median duration of 344.5 days from HAART initiation to HAART modification is comparable with a southern Indian study on generic HAART modification of 406 days [31] and a South African study of 14.9 months (447 days) [27]. This indicates that patients fared generally well on the initiating regimen for at least a year before modification of therapy. The modifications could therefore be due to persistent adverse drug events, policy changes or treatment failures.

Association Between Documented Adverse Drug Events and HAART Modification

The presence of documented adverse drug events was significantly associated with HAART modification [adjusted OR = 2.71 (95 % CI 2.11–3.48), p<0.001]. This is in conformation with results from other studies that also indicated that the experience of adverse drug events is a very common reason for HAART modification in HIV-positive patients on HAART therapy [6, 32–38]. Clearly, the issue of the relationship between occurrence of adverse drug events and HAART modification is an extremely important one that deserves further concerted study across several countries and with a larger number of patients, especially considering the fact that HIV has now become a chronic condition, with patients likely to be on life-long therapy. In addition, the proportion of patients experiencing an adverse drug event before therapy modification in this study is similar to the proportions found in studies by Padua et al. in Brazil [35] and Tadesse et al. in Ethiopia [37], which indicated that 56.1 and 53.8 %, respectively, of patients who modified to another therapy self-reported at least one adverse drug reaction [35, 37]. A similar case–control study in Ethiopia, however, showed that as high as 85.7 % of patients on HAART had changed therapy [32].

Clinical and Policy Implications

Adverse drug events associated with HAART have become a major public health concern, especially in relation to poor adherence to complex regimens in PLWHA [39]. Poor adherence to HAART due to experienced adverse drug events may even be prevalent regardless of the relationship of these events to HAART. It is therefore important to have an active pharmacovigilance programme in all HIV treatment programmes that permits the proper identification and characterisation of drug-related adverse events and to also develop approaches towards their management.

The presence of drug toxicity and/or poor medication adherence may limit any derived benefit from HAART and often results in therapy modifications which can be costly. HAART modification in resource-constrained settings like Ghana is costly as it narrows down on the regimen options available to patients, thereby posing a major challenge to the effectiveness of the ongoing treatment. This also poses challenges to the national programme, especially in the limited choice of regimens available to patients in this setting. In addition, although HAART modification could itself be an option for the management of adverse drug events, it can also lead to the development of new and severe adverse drug events, further complicating any future regimen options available.

In resource-limited settings, HIV clinics should closely monitor adverse drug events with both clinical and laboratory investigations in order to provide early interventions to mitigate any untoward HAART modification [31]. Most adverse drug events are determined clinically by the use of specific signs and symptoms, including fatigue with conjunctival pallor (due to ZDV-related anaemia), neuropsychiatric problems (due to EFV), peripheral wasting (due to d4T-related lipodystrophy) and rash (due to NVP, EFV or abacavir) [40]. At the KBTH, patients

undergo regular medical review, laboratory examinations, adherence counselling and general education on the disease and its management in order to overcome noncore HAART modifications. Adherence is reviewed at every clinic visit and documented, and is considered satisfactory when patients' self-report of compliance tallies with pill count. In addition, it will be important to establish standardised protocols for adverse drug event monitoring to improve the recognition, management and prevention of these events [41]. Management of adverse drug events including dose adjustment and the choice of appropriate regimen is a key strategy for improving adherence among HIV-positive patients on therapy and the avoidance of any subsequent therapy modification [42].

Tenofovir as an alternative to ZDV in potentially anaemic patients (baseline haemoglobin of 8–10 g/dL) is now the preferred first-option regimen choice in response to the toxic effects of ZDV. The finding that low CD4 counts (\150 cells/mm^3) at HAART initiation was associated with HAART modification in this study supports the current modified WHO recommendations that HAART should be started in patients with even high CD4 counts of 500 cells/mm^3 [43]. Adherence to this new WHO recommendation will ensure that patients initiated on HAART have lower odds of HAART modification and also the development of adverse drug events in the early stages of treatment. The current findings carry some clinical implications, which should be carefully considered in future studies, especially in African subjects who are prone to haemoglobinopathies and are more likely to develop adverse drug events with ZDV use [44]. The limited ARV regimen options may therefore present potential challenges to clinicians with time in resource-limited settings.

Limitations

A limitation of this study is that the findings cannot be generalised across all HIV treatment sites in Ghana since the study was localised to the KBTH. However, the literature review presents similarities with other studies done in Africa and beyond, thus rendering the study results worthwhile for any policy review. Self-reporting of adverse drug events by patients may have served as a limitation since the culture of spontaneous reporting of adverse drug events is absent in the African population and health professionals have to prompt reporting from most patients. Initial adherence counselling of patients should emphasise the reporting of all adverse drug events. Poor record-keeping practices also served as a limitation in retrieving complete data sets on patients; therefore, the use of electronic data capture should be encouraged.

This study is further limited by the lack of routine baseline viral load determination, which could have served to confirm treatment failure in some patients and therefore the need for therapy switch. This could have served also as a predictor of therapy switch since patients with very high viral load tend to have low CD4 count and often present with relatively more severe opportunistic infections. Owing to resource challenges, random primary HAART resistance testing is not carried out at baseline or in a failing regimen; therefore, we were unable to determine what possible effect primary resistance to the ARVs

in use might have had on our findings. Again no duplicate data extraction was done as it required another clinical pharmacist to be engaged specifically for that aspect of work, but efforts were made to ensure extracted data from the clinical folders matched with data from the electronic database.

CONCLUSION

These findings indicate that among HIV-positive patients on HAART, adverse drug events play a major role in treatment modifications (substitution or switch). Occurrence of adverse drug events may be used as a predictor for possible therapy modification. The institution of active pharmacovigilance in HIV treatment programmes permits the proper identification and characterisation of drug-related adverse events and can help to develop approaches towards their management and justified therapy modification. Monitoring adverse drug events and managing them appropriately may help to avoid dispensable therapy modifications.

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Chapter 3.2

INCIDENCE AND RISK FACTORS FOR TENOFOVIR-ASSOCIATED RENAL TOXICITY IN A COHORT OF HIV INFECTED PATIENTS IN THE KORLE BU TEACHING HOSPITAL, ACCRA, GHANA

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ABSTRACT

Background

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue widely recommended in international HIV treatment guidelines. The association of TDF with renal dysfunction has remained an area of interest. Purpose of study was to estimate the long term effects of TDF on renal profile and identify potential risk factors associated with renal impairment in Ghana.

Method

We selected 300 consecutive HIV-positive patients (with baseline creatinine clearance above 50 mL/min) who were initiated on TDF-based antiretroviral treatment in 2008 from a database capturing all patients on antiretroviral therapy at the Korle-Bu Teaching Hospital. Socio-demographic details, clinical characteristics, laboratory and antiretroviral regimens were collected from patients' medical records. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation at baseline and as per institutional guidelines for renal function test. Renal impairment was defined as a reduction in CrCl to values between 30 mL/min and 49.9 mL/min (moderate renal impairment) and below 30mL/min (severe renal impairment). The proportion of patients with moderate or severe renal impairment was calculated. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for factors associated with renal impairment.

Results

Median follow up time was 2.9 years (interquartile range (IQR) 2.3-3.4 years) for the 300 study participants. Females were dominant (n=213, 71.1%) and the mean age of study participants was 39.1 ± 11.1 years. The median CrCl rate at initiation of TDF-containing ART was 76.8 mL/min [IQR 58.3-105.4]. At study endpoint, 63 participants (21.0% [95% CI: 6.5-26.1]) recorded CrCl rate below 50ml/min indicating incident renal impairment, made up of 18.3% moderate renal impairment and 2.3% severe renal impairment. Factors associated with the incidence of renal impairment were increasing age (RR=1.04 [95% CI, 1.03-1.06]) per year, decreasing creatinine clearance rate at baseline (RR=1.05 [95% CI, 1.04-1.08] per every 1 mL/min decrease), WHO HIV stage III (RR=3.78 [95% CI, 1.42-10.06]) or Stage IV (RR=3.42 [95% CI, 1.16-10.09]) compared with stage I and participants with BMI of <18.5kg/m^2 underweight (RR=3.87; 95% CI, 2.49-6.03) compared with patients with BMI of >18.5-24.9 kg/m^2 (normal weight).

Conclusion

The use of TDF based regimen led to 18.3% developing moderate renal impairment and 2.3%, severe renal impairment. Patients with identified risk factors, i.e. older age, decreasing baseline CrCl, WHO HIV stage III or IV and BMI <18.5 kg/m^2, should be targeted and monitored effectively to prevent renal injury.

INTRODUCTION

Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) are pertinent issues globally, more so in sub-Saharan region of Africa and in Ghana [1]. According to the World Health Organization, there were approximately 35 million people worldwide living with HIV/AIDS in 2013. Sub-Saharan Africa was the most affected region, with 24.7 million people living with HIV [1]. The Ghana Aids Commission in 2013 reported the prevalence of HIV to be 1.3% as against 3.6% in 1999 [2]. Ghana has therefore seen great decrease in the prevalence rate of HIV over a decade. This significant reduction in prevalence could be attributed to the awareness created through the activities of the National AIDS/STI Control Program (NACP) and the benefits accruing from the life prolonging anti-retroviral drugs (ARV), which also reduces the degree of infectivity of HIV positive patients on subsidized or free highly active antiretroviral therapy (HAART) [3]. HAART has reduced the mortality and morbidity associated with HIV infection and the risk of HIV-infected patients' progression to AIDS [4]. These ARVs are expected to be taken throughout the patient's life time once the decision to initiate HAART is made.

Side effects have been reported by patients on these drugs, similar to other chronically administered drugs. ARVs have documented side effects and adverse drug reactions ranging from mild to life threatening ones with their effect being transient or prolonged [3]. Complications related to long-standing HIV infection and treatment, such as the nephrotoxic effects, increase morbidity and mortality of patients. HAART can itself cause renal toxic effects directly by inducing acute interstitial nephritis, crystal nephropathy, renal tubular disorders and indirectly through possible drug interactions [5].

Tenofovir disoproxil fumarate is an orally bioavailable prodrug of tenofovir, an acyclic nucleotide analogue reverse-transcriptase inhibitor (NtRTI), widely used in the treatment of HIV infection and also approved for treatment of Hepatitis B virus infection. Tenofovir is preferred in most consolidated antiretroviral therapy (ART) guidelines [6] in preference to the use of stavudine and zidovudine because of better tolerance, low frequency of adverse events and a once daily dosing combination of tenofovir, lamivudine or emtricitabine and efavirenz [6]. Concerns regarding nephrotoxicity were initially raised by the structural similarity between tenofovir and the nephrotoxic acyclic nucleotide analogues adefovir and cidofovir [7]. These two drugs cause proximal tubulopathy, possibly in part due to decreasing mitochondrial DNA (mtDNA) replication through inhibition of mitochondrial DNA polymerase [8]. As shown in a study carried out by Copper et al, the use of ART regimens containing tenofovir produces a loss in renal function which is statistically significant but its clinical effect is modest [9]. The mechanism by which tenofovir produces its nephrotoxicity is not well known. However, Kohler *et al.,* (2009) speculated that tenofovir causes renal dysfunction by inducing mitochondrial toxicity [10]. A retrospective study of 1647 patients who started TDF based regimen found a steeper decline in estimated glomerular filtration rate (eGFR) compared with those who started with non TDF based regimen [11]. Another study of 324 patients who started ARV treatment on TDF based regimen found a greater

incidence of proximal tubular dysfunction and worsening decline in eGFR over 24 months [11]. Much against the evidence above, a randomized study of abacavir (ABC) and lamivudine (3TC) against tenofovir and emtricitabine (FTC) in 333 persons found no statistical significant differences in eGFR over 48 weeks [12].

Although the use of tenofovir in a TDF based regimen is a preferred first-line ART regimen in Ghana, renal outcomes among patients receiving this option require further investigation in Ghana as well as Sub Saharan Africa with respect to the above stated effects of TDF on the kidneys. Available evidence points to a 10 to 15% prevalence rate of renal impairment in the general African adult population, thereby exposing them to a much higher risk of renal damage over time [22]. A study by De Waal et al in South Africa [13] involving 15156 participants using TDF reported that eGFR increased for participants with baseline eGFR >90ml/min but decreased for those <90ml/min whereas for those below<60ml/min about 1.9% developed severe renal impairment with eGFR <30ml/min. Associated risk factors identified included older age, baseline eGFR< 60ml/min, CD4 count <200 cells/uL, body weight <60kg and use of protease inhibitor (PI). Another study from Lesotho reported that in their setting, TDF-associated renal toxicity was rare and mainly transient in patients. Risk factors associated with declining CrCl were older age, women, and patients with severe immunosuppression [14]. Although the incidence of TDF-related kidney dysfunction seems to be low in most settings, the effect of TDF on renal profile in patients starting ART with varying levels of renal function has not been studied previously in our setting. World Health Organisation (WHO) in its 2015 consolidated guidelines, recommended the initiation of HAART irrespective of CD4 count [15], and in Ghana, the ART guidelines indicated TDF-based regimens as the recommended preferred first-line antiretroviral therapy for patients [16], additionally the monitoring of TDF based therapy was not compulsory [15]. It is against this background that this research was undertaken to study changes in renal function over time in patients on tenofovir based antiretroviral regimen in our patient population at a tertiary hospital in Ghana. We investigated the incidence of renal impairment in HIV positive patients treated with TDF based regimen and identified associated potential risk factors.

METHODS

Study Setting

The Korle Bu Teaching Hospital is a public university tertiary hospital with 2000 beds in Accra, Ghana. The population for this study consisted of HIV positive patients captured in the database used in providing services to patients at the Fevers Unit which is linked to the pharmacy department where patients present for their medications. The study was limited to patients initiated on tenofovir-based regimen within the study period.

Study Design

We undertook a retrospective cohort study of 300 consecutive patients (with baseline creatinine clearance rate of ≥50 mL/min) who started tenofovir based regimen from

January 2008 with study end-point at December 2013. A clinical research form was used to collect data from patients' folders. This instrument was developed by the research team, piloted for reliability and validity. The form was organised into four sections; section A dealt with the demographic characteristics of respondents; section B, the patient's medical characteristics; section C focused on the patient's antiretroviral therapy; and section D with patient's adherence characteristics.

The data collection form was pre-tested on 20 folders to remove items not deemed necessary to the expected outcomes. Data of primary interest were demographics, serum creatinine and urea at baseline, weight, tenofovir based regimens, HIV serotyping and CD4 count at baseline. Other information of secondary interest included were co-morbidities and co-medications. Patients were followed up from the study start point of January 2008 until renal impairment, death, or 31st December 2013, whichever came first. Absolute change in creatinine clearance (CrCl) using the Cockcroft-Gault equation was calculated at baseline and as per institutional guidelines for renal function test. Renal impairment was defined as a reduction in CrCl below 50 mL/min (moderate renal impairment) and below 30mL/min (severe renal impairment).

Statistical analysis

Descriptive and univariate analysis were conducted for demographic, clinical and laboratory characteristics established for the study. Patients' demography was described using mean ± standard deviation (SD) for continuous variables and percentages for categorical data. Statistical significance of differences between any two groups was tested using appropriate parameters to compare and measure associations. A p-value of <0.05 was considered significant. Univariate analysis was done to identify risk factors associated with renal impairment (age, sex, BMI, WHO HIV stage, CD4, TDF regimen type) and reported as relative risk (RRs) and 95% confidence intervals (CIs).

RESULTS

A total of 300 patients with estimated baseline creatinine clearance of >50 mL/min and initiating TDF containing ART were included in the study. Mean age of the study participants was 39.2 ± 11.1 years and 71.7% (n=101) were female (Table 1). Baseline BMI of <18.5 kg/m^2 was present in 17.3% (n=52) of the study participants. The prevalence of smokers among participants was 3.7% (n=11) and 13.7% (n=41) reported that they drank alcohol (Table 1).

Table 2 shows the clinical characteristics of the study participants. Majority of the study participants (97.0%, n=291) were administered TDF in combination with a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI, either efavirenz or nevirapine. Median creatinine clearance rate before initiation of TDF containing ART was 76.8 mL/min [Interquartile range (IQR) =58.3-105.4] and median duration from initiation of TDF containing ART to study end-point or censoring was 2.9 years [IQR=2.3-3.4]. The most frequent co-morbidities reported were pregnancy (7.3%), anaemia (3.3%) and tuberculosis (3.3%). A total of 40 (13.3%)

Table 1. Socio-demographic characteristics of study participants

Characteristics	N=300 n, %
Age, mean ± SD, years	39.2 ± 11.1
Gender	
Female	215 (71.7)
Male	85 (28.3)
Marital status	
Single	104 (34.7)
Married/cohabiting	163 (54.3)
Divorced/separated/Widowed	33 (11.0)
Baseline BMI (kg/m^2)	
<18.5	52 (17.3)
18.5-24.9	194 (64.7)
≥25.0	54 (18.0)
Educational status	
None	45 (15.0)
Primary/Basic	136 (45.3)
Secondary	83 (27.7)
Tertiary	36 (12.0)
Occupation	
Unemployed	33 (11.0)
Self-employed	200 (66.7)
Public/Private employment	67 (22.3)
Smoking of tobacco	
Yes	11 (3.7)
No	287 (96.3)
Alcohol use	
Yes	32 (10.7)
No	268 (89.3)
Source of funding	
Self	154 (51.3)
Health insurance	146 (48.7)

study participants were on medication other than antiretrovirals and the most frequent co-medications were antibiotics (7.0%) and antihypertensive (4.3%). At study end-point, 63 study participants (21.0%; 95% CI, 6.5-26.1) were classified as having renal impairment with CrCl rate <50.0 mL/min. Seven study participants (2.3%) were further classified as having severe renal impairment with CrCl rate <30.0 mL/min.

Table 3 shows the factors associated with incident renal impairment. Age was associated with renal impairment such that for every 1 year increase in age, the risk of renal impairment increased by 4% (RR=1.04; 95% CI, 1.03-1.06; p<0.001). Similarly, decreasing baseline creatinine clearance rate was associated with renal impairment, such that for every 1 mL/

Table 2. Clinical characteristics of study participants

Characteristics	N=300 n, %
Duration on TDF (study endpoint/ censoring), median (IQR) years	2.9 [2.3-3.4]
Baseline CrCl rate, median (IQR), mL/min	76.8 [58.3-105.4]
WHO HIV stage	
Stage I	52 (17.3)
Stage II	76 (25.3)
Stage III	134 (44.7)
Stage IV	38 (12.7)
HIV type	
Type I	284 (94.7)
Type II	16 (5.3)
ART regimen administered	
NNRTI-based	291 (97.0)
PI-based	9 (3.0)
Baseline CD_4 count (cells/mm^3)	
<150	134 (44.7)
150-250	58 (19.3)
>250	108 (36.0)
Adverse event	
Present	47 (15.7)
Absent	253 (84.3)
Co-morbidities[1]	
None	220 (68.0)
Pregnancy	22 (7.3)
Anaemia	10 (3.3)
Tuberculosis	10 (3.3)
Hypertension	9 (3.0)
Malaria	9 (3.0)
Pneumonia	8 (2.7)
Hepatitis	7 (2.3)
Cerebral toxoplasmosis	6 (2.0)
Urinary tract infection	5 (1.7)
Asthma	2 (0.7)
Diabetes	2 (0.7)
Achalasia	1 (0.3)
Deep Vein Thrombosis	1 (0.3)
Gouty arthritis	1 (0.3)
Psychosis	1 (0.3)
Co-medication[1]	
None	260 (86.7)
Antibiotic	21 (7.0)
Antihypertensive	13 (4.3)
Haematinic	5 (1.7)

Table 2. (continued)

Characteristics	N=300 n, %
Antiallergic	3 (1.0)
Anticoagulant	2 (0.7)
Antidiabetic	2 (0.7)
Antigout	1 (0.3)

[1]% may not add up to 100; ART=Antiretroviral therapy; CrCl=Creatinine clearance rate; NNRTI=Non-nucleoside reverse transcriptase inhibitor; PI=Protease inhibitor; TDF=Tenofovir

min decrease in baseline CrCl rate, the risk of incident renal impairment increased by 5% (RR=1.05; 95% CI, 1.04-1.08; p<0.001) (Table 3). Patients with WHO HIV staging of either Stage III (RR=3.78; 95%CI 1.42-10.06; p<0.001) or Stage IV (RR=3.42, 95%CI 1.16-10.09; p<0.026) at initiation of TDF-containing ART, were at increased risk of incident renal impairment compared with patients of Stage I (Table 3). In addition, patients with baseline BMI of <18.5 kg/m^2 (underweight) were also at increased risk of incident renal impairment compared with patients with BMI of 18.5-24.9 kg/m^2 (normal weight) (RR=3.87; 95% CI, 2.49-6.03; p<0.001) (Table 3).

DISCUSSION

We found that approximately 1 out of 5 patients on tenofovir based regimen from the Korle Bu Teaching Hospital HIV Clinical Care program experienced development of renal impairment over the 5 years period of this study. It is worth noting that of these about 2.3% developed severe renal impairment. Factors associated with the incidence of renal impairment were older age, lower CrCl at baseline, WHO HIV stages III and IV compared to those with stage I and baseline BMI below 18.5kg/m^2.

Similar studies have also reported changes in CrCl over time irrespective of whether estimated glomerular filtration rate (eGFR) was determined using Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) but with varying incidences [11,12,17,18]. The Incidence of renal impairment in these references after initiation of TDF based regimens is varied but tended to be lower than the incidences observed in this study. This could be due to different methodological approaches used or varying renal impairment incidences in different populations, The clinical implication is not certain but it is proven that patients on tenofovir based regimen tend to develop decreases in renal performance as compared to those on non- tenofovir based regimens [9]. However, a Japanese retrospective study of 493 patients initiated on TDF based regimen reported similar incidence of declining renal function [21], comparable with this study.

Review of other studies revealed some risk factors associated with renal impairment in the use of TDF based regimens. These included older age, declining CD4 levels, nephrotoxic

Table 3. Factors associated with renal impairment in a cohort of patients attending HIV clinic at the Korle-Bu Teaching Hospital in Accra, Ghana

Characteristic		Renal impairment N=63 n, %	No renal impairment N=237 n, %	Relative risk [95% CI]	p-value
Age, mean ± SD, years		45.3 ± 12.15	37.6 ± 10.3	1.04 [1.03-1.06]	<0.001
Baseline CrCl rate, median (IQR), mL/min		55.7 [52.4-66.1]	85.7 [66.9-113.2]	0.95 [0.93-0.96]	<0.001
Gender	Male	18 (28.6)	67 (28.3)	1.01 [0.62-1.64]	0.962
	Female	45 (71.4)	170 (71.7)	1.00	
Smoke tobacco	Yes	2 (3.2)	9 (3.8)	0.86 [0.24-3.06]	0.810
	No	61 (96.8)	226 (96.2)	1.00	
Alcohol use	Yes	4 (6.4)	28 (11.8)	0.57 [0.22-1.46]	0.240
	No	59 (93.6)	209 (88.2)	1.00	
WHO HIV stage	Stage IV	4 (6.3)	48 (20.2)	3.42 [1.16-10.09]	0.026
	Stage III	10 (15.9)	66 (27.9)	3.78 [1.42-10.06]	0.008
	Stage II	39 (61.9)	95 (40.1)	1.71 [0.57-5.16]	0.341
	Stage I	10 (15.9)	28 (11.8)	1.00	
HIV type	Type II	2 (3.2)	14 (5.9)	0.58 [0.16-2.17]	0.420
	Type I	61 (96.8)	223 (94.1)	1.00	
ART regimen administered	PI-based	2 (3.2)	7 (3.0)	1.06 [0.31-3.67]	0.927
	NNRTI-based	61 (96.8)	230 (97.0)	1.00	
Baseline CD_4 count (cells/mm^3)	<150	30 (47.6)	104 (43.9)	1.42 [0.83-2.44]	0.200
	150-250	16 (25.4)	42 (17.7)	1.75 [0.96-3.20]	0.068
	>250	17 (27.0)	91 (38.4)	1.00	
Presence of co-morbidity	Yes	20 (31.7)	60 (25.3)	1.28 [0.80-2.04]	0.299
	No	43 (68.3)	177 (74.7)	1.00	
On co-medication	Yes	12 (19.1)	28 (11.8)	1.53 [0.90-2.61]	0.119
	No	51 (80.9)	209 (88.2)	1.00	
Baseline BMI (kg/m^2)	<18.5	27 (42.8)	25 (10.5)	3.87 [2.49-6.03]	<0.001
	≥25.0	10 (15.9)	44 (18.6)	1.38 [0.71-2.68]	0.340
	18.5-24.9	26 (41.3)	168 (70.9)	1.00	
Adverse event	Present	12 (19.1)	35 (14.8)	1.27 [0.73-2.19]	0.397
	Absent	51 (80.9)	202 (85.2)	1.00	

ART=Antiretroviral therapy; BMI=Body mass index; CrCl=Creatinine clearance; IQR=Interquartile range; NNRTI=Non-nucleoside reverse transcriptase inhibitor; PI=Protease inhibitor; SD=Standard deviation

drug use at the same time, gender and advanced HIV disease [20,22]. Our results did not establish an association with declining CD4 levels and gender, but supported association with lower baseline CrCl, BMI of below 18.5kg/m at initiation, worsening immune suppression represented by WHO HIV stages 3 and 4 and older age. Some authors reported female gender as a cause of higher blood levels of TDF leading to renal toxicity [23], but

a population study in Europe did not find female gender as a predictor of renal toxicity [24]. A study from Lesotho however found that women were at risk of decreasing CrCl after long term exposure to tenofovir based regimen [14].

Lower BMI of <18.5kg/m^2 was evident in 17% of the participants at baseline and it was found to be associated with incident renal impairment which is similar to earlier reports [21,22]. Although findings from this study indicate no association between type of TDF regimen administered (TDF- based regimen with protease inhibitors lopinavir/ritonavir or TDF-based regimen with non-nucleoside inhibitors efavirenz or nevirapine) and renal impairment, other studies reported that the degree of renal function decline was more frequent and more serious in TDF- based regimen with protease inhibitors lopinavir/ritonavir than TDF-based regimen with non-nucleoside inhibitors (efavirenz or nevirapine) [25,26]. This is supported by studies which indicated that TDF excretion in the urinary lumen is partly inhibited by lopinavir and ritonavir leading to accumulation of TDF and hence the possible injury to the kidneys [26, 27]. The number of patients on TDF-based protease inhibitor regimen in our study was however low and therefore could account for the lack of association between type of TDF-based regimen and renal impairment.

Fifty-seven percent (57%) of participants were found to have WHO Stage III and IV disease and this was found to be associated with declining renal performance. Literature supports this finding as worsening HIV disease results in various opportunistic infections that worsen kidney performance [27]. In this study CD4 levels were below 150 cells/mm^3 in 44% of participants but this was not established to be associated with incidence of renal impairment in our cohort of patients. This is at variance with other findings from Sub Saharan Africa which emphasized association between CD4 levels <50 cells/mm^3 and renal impairment [13,14]. Older age was established to be associated with renal impairment in our study analysis and this is consistent with other studies which associated older age with low baseline CrCl [22,25,27].

TDF is presently recommended as the preferred first–choice therapy in Ghana and in many other African countries where HIV prevalence is relatively high because of its better tolerance, low frequency of adverse events, and compatibility with other drugs resulting in single daily dosing formulations [6]. TDF based regimen is therefore preferred to other antiretroviral therapy options and with the recent 90/90/90 target declaration by WHO, the question of whether long term usage will pose major problems for the more African HIV positive patients who are likely to be initiated on TDF in resource limited settings is paramount. The determination of about 20% renal impairment in this study gives an indication of possible problems in future, more so with the WHO recommendation of "Treat All" [15, 16], irrespective of CD4 and laboratory monitoring of baseline renal performance. This finding evidently calls for prudent monitoring of all patients on TDF based regimen with CrCl below the normal range of >80ml/min [14,17]. The incidence of renal impairment comes against a background of determined prevalence of 10% renal impairment in all medical admissions as reported in the Korle-Bu Teaching Hospital's 2012 Annual Report [28]. In this context, the issue of long-term nephrotoxicity is important and much can be achieved

in reducing this risk by health professionals observing operational norms as recommended by protocols and guidelines provided for use. On a large scale as pertains in the National HIV Programme, lack of adequate and skilled human resources, equipment and reagents for checking of creatinine clearance remains a hurdle to contend with. It is recommended therefore that simple and feasible renal screening tests like dipstick testing for urine protein be implemented [29]. Patients with positive urine protein testing on dipstick can then be offered serum creatinine testing. This offers a cheaper and a quicker screening tool which can easily be deployed in all rural and deprived areas for initial screening to eliminate patients with the potential to develop renal discomfort when initiated on TDF based regimen. Measuring renal function carefully to assess possibility of renal disease before prescribing TDF based regimen for the higher risk patients as indicated by the findings of this study should be a yardstick for initiating ART irrespective of the" treat all "policy since our primary concern is to protect patients from renal injury. The study observed that patients classified at baseline as WHO stages 3 and 4 and those with lower BMI as specified in the study report should have baseline renal assessment done before the initiation of TDF based therapy. In the absence of laboratory facilities in rural areas or unaffordability, other regimen types could be considered. Presently the only alternatives to tenofovir are abacavir and zidovudine but these 2 NRTIs also have their limitations with regard to patients' clinical characteristics.

The unavailability of creatinine and urea recordings regularly is considered a limitation to this study. We had to use available recordings as and when available in the medical folders and the database. Despite a sample size of 300 which limited us in assessing the association between the various TDF-based regimen types and renal impairment and also conduct a multiple regression analysis of the factors associated with renal impairment, this study adds to the growing concern on the need to continually monitor patients on TDF-based regimen for early detection of renal impairment.

CONCLUSION

The use of TDF based regimen as first line ART regimen in Ghana and most African countries is justified by its beneficial attributes. However, the incidence of renal impairment of 1 in every 5 patients with 3% with the group developing severe renal impairment on TDF-based ART as determined in this study supports the argument of requesting for laboratory support before initiating TDF despite our resource challenged circumstances. Additionally, all patients started with TDF based regimen in response to the Treat All or the 90/90/90 target by 2020 policy initiative by WHO should be monitored in time while on ART to prevent untoward effects.

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Chapter 3.3

KNOWLEDGE AND ATTITUDES OF HIV INFECTED PATIENTS ON THE ADVERSE EFFECTS OF ANTIRETROVIRAL MEDICINES IN GHANA

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ABSTRACT

Background

Antiretroviral therapy (ART) is effective in reducing morbidity and mortality in patients living with HIV/AIDS. However, adverse effects to antiretroviral therapy pose major problems and threaten adherence to therapy. We evaluated the knowledge and attitudes of patients to antiretrovirals following routine adherence counselling and education in the Korle Bu Teaching Hospital in Accra, Ghana.

Method

This cross-sectional study was conducted by administering a questionnaire on socio-demographics, knowledge of adverse effects (AEs) of antiretrovirals and attitude to adverse effects to 98 patients who were on antiretroviral therapy. A 3 point Likert-scale was used to assess knowledge of adverse effects of antiretrovirals and a 5 point Likert-scale to assess attitudes to adverse effects. Mean rated scores for attitude to adverse effects were estimated and factor analysis was used to reduce the dimensions of the attitudes observed to identify relevant latent constructs.

Results

Sixty-one percent of participants were females and most of the participants were aged 35-44 years (35%). Ninety-nine percent of participants answered that they had been counselled on unpleasant effects of their medicines and 93% knew that all medicines could cause some unpleasant effects. Concerning attitude, 90% of study participants strongly agreed that they benefit from their medicines and get better taking them (mean rated score=4.87 ± 0.49) whilst 27% strongly agreed that the medicines may have side effects (mean rated score =3.12 ± 1.55). Majority of the study participants (74%) strongly disagreed that there was no need to tell their doctor/pharmacist about adverse effects to antiretrovirals (mean rated score =4.60 ± 0.83). Factor analysis yielded two underlying dimensions (cognitive and behavioural/affective aspects) that described participants' attitude towards adverse effects. These are.

Conclusions

Study participants rating for participants' knowledge on AEs was good and exhibited positive attitudes to AEs of ART. Adherence counselling and education provided to patients living with HIV/AIDS before initiation of antiretroviral therapy is beneficial and should be continued.

INTRODUCTION

Antiretroviral therapy (ART) has been very effective in reducing rates of morbidity and mortality in patients living with HIV/AIDS [1-3]. If started early or the right time, current ART substantially reduces HIV-related morbidities, lowers risk to premature death and improves the quality of life for prolonged periods. The viral suppressive effect of ART leads to reductions in infectivity and lowered likelihood of disease transmission among sexual partners. These attributes and benefits are strong infection prevention paths of HIV therapy [4,5] and have resulted in improved health seeking attitudes in patients leading to an improved quality of life for patients living with the condition.

Antiretroviral therapy improves the quality of life of patients and also reduces mortality and morbidity, but adverse effects (AEs) accompanying the use of ARVs can deter treatment, impact quality of life and impede adherence to ARVs [6]. These AEs from ART are often linked to lower levels of medication adherence and result in discontinuation of otherwise appropriate and effective therapy [7]. Adherence counselling sessions with patients normally focus on known AEs associated with specific ARTs in use, and therefore this study reported on such AEs. Early onset of adverse effects of ARVs include gastrointestinal such as diarrhoea, nausea, vomiting and flu-like symptoms, headache, dizziness, vivid dreams, rash and hepatitis [7].

Some studies have shown that there are significant deficits in patients' knowledge of their medications and their adverse effects while others reported good knowledge [8-10]. Patients' good or poor perceptions on AEs result in attitudes, which positively or negatively affect the benefits of antiretroviral therapy or lead to poor compliance and discontinuation in the management of HIV. In addition, AEs could impact physically and psychologically on patients resulting in the development of attitudes like the avoidance in seeking treatment, reporting AEs or deciding to use alternative medicines on their own.

Knowledge is defined as facts, information, and skills acquired through experience or education; the theoretical or practical understanding of a subject [11]. A study conducted in Gabon [12], concluded that patients want to be provided the complete drug information including the side effects and any difficulties that could be experienced. Another study supported the fact that we need to educate and manage the AEs of medicines on patients to motivate and retain them in chronic disease treatment [13]. Generally, patients dislike the discretion of health professionals to pick and choose when to educate them about their clinical condition or the medicines they are being given [14].

An attitude is defined as "a relatively enduring organization of beliefs, feelings, and behavioural tendencies towards socially significant objects, groups, events or symbols" [15] and has a structure which can be described in three ways. First, an affective component involving one's feelings and emotions, e.g. "I am afraid of the AEs of my medicines." Second, a behavioural component where one acts as a result of e.g. "I will not persist in taking my medicines" and third the cognitive aspect which involves one's knowledge/ beliefs about an attitude object like medicines e.g. "I get better when I take my medicines". Even though,

every attitude has these three components, an individual's particular attitude can reflect one of the components more than the others. We can therefore summarise these components as affective based, behavioural based and cognitively based attitudes. These components of attitude emerged in studies of adherence, where non-adherence has been linked to several outcomes. These outcomes include doubts on treatment efficacy, concerns about side effects as well as long-term toxicities, challenges associated with meeting scheduling demands and personal capacity to adhere to treatment. Also, concerns about the impact of ART on self-identity, and the possibility of treatment leading to disclosure of one's HIV status [8,16,17].

Several studies have been conducted to assess the knowledge, attitudes, and practices of patients as regards AEs to ART [18-20]. A study in Nigeria [21] reported good knowledge of AEs and positive attitudes, whereas another study [10] reported significant deficits in patients' knowledge leading to poor attitudes culminating in discontinuation of therapy. Another study in Nigeria concluded that respondents with good knowledge about the AEs of ARTs present positive attitudes, which results in better adherence to ART than those with poor knowledge [22].

Since 2003, when antiretroviral services were introduced in Ghana, no study has been done to assess the knowledge, attitude and practices of PLWHA to AEs of ART at the KBTH. The present study therefore is aimed at improving patient care by investigating the level of knowledge, the attitudes and practices of these patients with a view to identify any gaps in their knowledge which could be affecting their behaviours. We adopted a similar approach to the study carried out in Nigeria [21] but emphasized on three different components of attitude namely affective, behavioural and cognitive. We used factor analysis to help identify and differentiate these components.

MATERIALS AND METHODS

Study area

The study was carried out in the Fevers Unit and the Pharmacy Department of the Korle Bu Teaching Hospital in Accra, Ghana.

Study design

This is a cross-sectional study. We collected primary data from answers to questionnaires served on HIV patients attending review clinics at the Korle-bu Teaching Hospital, to evaluate their knowledge and attitudes on the antiretroviral therapy (ART) they receive. Participants had received routine adherence counselling and education.

Study population

About 10,000 patients living with HIV/AIDS receive ART from the Korle Bu Teaching Hospital. From this number, about 1000 patients are attended to monthly. The sample size was determined by the assumption that at least 10 study participants for each questionnaire

items used as proposed by Nunnally [23]. Based on the 6-questionnaire items used for attitude to the adverse effects of HIV medicines, 15 study participants were sampled for each of the attitude questionnaire item giving a minimum sample size of 90 study participants. A total of 100 patients were sampled as study participants for this study. Patients were approached on three clinic days of Mondays, Wednesdays, and Fridays weekly for a month. Ten patients were randomly selected from the list of patients' attendance on that day. All adult HIV-positive patients above the age of 18 years currently receiving ART at the pharmacy department for more than six months and who agreed to sign informed consent form were eligible for the study. Study participants were recruited and administered the questionnaire at the Pharmacy Department of the Korle-Bu Teaching Hospital.

Data collection methods and instruments

An 18-item questionnaire with a 3-point Likert-scale format was used to assess knowledge of AEs of ARVs and a 5-point Likert-scale to assess attitudes to AEs. The study instrument covered three sections namely socio-demographic information (6-questionnaire items), knowledge of adverse effects of HIV medicines and proposed action if participants were to experience such AEs (6-questionnaire items), and attitude to the adverse effects of HIV medicines (6-questionnnaire items). The administration of the instrument to study participants was done by the study team.

Data analysis

Data analysis was done using SSPS version 16. Descriptive statistics of the responses were estimated. Chi-square test was conducted to test differences between socio-demographic variables among participants. *P* values were two-tailed and $P < 0.05$ used to determine statistical significance.

The Likert rating scale used was: strongly disagree =1, disagree =2, neutral =3, agree =4 and strongly agree =5. The negatively worded items were reverse coded so that higher scores represent higher knowledge and attitudes. Rated attitude scores were treated as interval data suited for quantitative analysis. Rated score means (RSM) were computed for each of the six individual questionnaire attitude items by summing individual scores for that questionnaire item and dividing by the total number of participants who responded to that questionnaire item. An average midpoint for all the six questionnaire items (on attitude to adverse effects of HIV medicines) was calculated as the sum of the RSMs calculated divided by the six questionnaire items. Individual questionnaire items with RSM above the average midpoint were regarded as positive attitudes while below the mid-point were considered as negative attitudes [21]. To confirm whether the questionnaire items generated responses associated to other constructs that could not be directly measured; we conducted a confirmatory factor analysis, a data reduction tool which removes duplication from a set of correlated variables. We first used the Kaiser–Meyer–Olkin (KMO) measure to determine whether the sampling was adequate for factor analysis. KMO values greater than 0.5 are termed adequate, whilst

values of 0.7 and 0.8 are considered good. Values greater than 0.90 are rated as "superb" for factor analysis [24]. Bartlett's test of sphericity was also performed. A value less than 0.05 indicate that a factor analysis may be useful with the obtained variables. Factor analysis was performed using principal components extraction [25] and varimax rotation with Kaiser normalization. Factors selected for rotation had eigenvalues greater than 1. The relationship of each variable to the potential underlying construct is expressed by the factor loading, which can be interpreted in a similar way as standardized regression coefficients. Items with factor loadings greater than or equal to 0.40 were considered important, and loadings of 0.50 or greater were considered very significant [25]. Reliability analysis was performed to determine the internal consistency of the questionnaire using Cronbach's alpha.

Ethical clearance

Ethical permission was obtained as part of the ongoing research work on the pharmacovigilance of antiretroviral medicines in use on patients living with HIV/AIDS from the College of Health Sciences, University of Ghana Ethical and Protocol Review Committee [MS-Et/M.6-P.5.3/2009-10]. Written consent was also obtained from each study participant.

RESULTS

Of the 98 study participants, 61% (n=60) were female, 35% (n=34) were between the ages of 35-44 years old; 49% (n=48) were married, 78% (n=76) were Christians with 60% (n=59) having completed secondary/tertiary education. A total of 61% (n=60) reported to be self-employed (Table 1).

Of the 98 participants, 99% (n=97) reported to have been counselled on the AEs of their medicines: 93% (n=91) said they knew that all medicines cause AEs irrespective of how good they were and a 65% (n=64) were aware of the AEs of their ARVs and what to do in the event of AEs (Table 2). Majority of the patients 82% (n=80) indicated they will report suspected AEs to their healthcare professional whilst a few 6% (n=6) indicated that they will choose other drugs to administer by themselves; 5% (n=5) were not prepared to do anything but relax and wait whilst 2% were prepared to use herbal medicines to treat AEs (Table 3).

Participant's knowledge of AEs in terms "all medicines irrespective of how good they are can cause some AEs", "knows unpleasant effects of ARVs" and "knowledge of what action to take when participants experience AEs" had no association with gender, educational status, age, religion, marital status and type of occupation (data not shown).

Concerning attitudes, 90% (n=88) strongly agreed that they benefit from their medicines with 36% agreeing that sometimes medicines have AEs which can worsen health conditions. However, a majority of patients (81%) strongly disagreed that AEs were their problem for which they should worry about and take responsibility, indicating positive attitude. Majority of patients (74%) also strongly disagreed that they will stop their medication if they know the AEs associated with them indicating positive attitude (Table 4). The estimated

Table 1. Demographic characteristics of respondents (N=98)

Characteristic	N	%
Gender		
Female	60	61
Male	38	39
Age (years)		
25-34	16	16
35-44	34	35
45-54	29	30
55-64	17	17
> 64	2	2
Marital status		
Single	24	24
Married	48	49
Divorced/Widowed/Separated	26	27
Religion		
Christianity	76	78
Muslim	22	22
Level of formal education		
None	10	10
Basic/Primary	29	30
Secondary	34	35
Tertiary	25	25
Type of occupation		
Unemployed	7	7
Self-employed	60	61
Formal employment	28	29
Others	3	3

Table 2. Knowledge of adverse effects of HIV medicines as reported by respondents (N=98)

	Yes n (%)	No n (%)	Not sure n (%)
Were you educated about your clinical condition?	97 (99)	0 (0)	1 (1)
Were you counselled on the unpleasant effects of your medicines?	97 (99)	1 (1)	0 (0)
Do you know that all medicines irrespective of how good they are can cause some unpleasant effects?	91 (93)	4 (4)	3 (3)
Do you know the unpleasant effects of the particular medicines you are taking for your condition?	64 (65)	21 (22)	13 (13)
Do you know what to do when you experience some of these unpleasant effects suspected to be caused by your medicines?	69 (71)	16 (16)	13 (13)

Table 3. Participants reported actions when they experience unpleasant effects to medicines

If you know what to do when you experience unpleasant effects suspected to be caused by your medicines, please tell us? (N=98)	Response, n (%)		
	Yes	No	Not sure
Report to healthcare provider (doctor, pharmacist, etc.) at the hospital	80 (82)	1 (1)	2 (2)
Take another drug(s) to treat the suspected adverse effects	6 (6)	0 (0)	0 (0)
Relax and do nothing as the adverse effects will resolve as my body gets used to the medicines	5 (5)	1 (1)	0 (0)
Change the drug(s) suspected to cause the adverse effects of my medicines	(0)	0 (0)	0 (0)
Reduce the dose of the drug(s) suspected to cause the adverse effects	1 (1)	0 (0)	0 (0)
Use local herbal medicines to treat suspected adverse effects	2 (2)	0 (0)	0 (0)
Total	94	2	2

average midpoint for all RSMs was 4.31. The RSMs were higher than the midpoint of 4.31 in questionnaire items 1, 3, 4 and 6, indicating positive attitudes whereas they were lower for items 2 and 5, denoting negative attitudes (Table 4).

Factor analysis of the six questionnaire items yielded two underlying dimensions of attitude towards AEs of ART by patients with Eigen value of 1.0. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.669, and the Bartlett test of sphericity was statistically significant ($p<0.001$), both confirming adequacy of the sample size for factor analysis. The internal consistency of the six questionnaire item attitudinal scale as measured by Cronbach's alpha was 0.531.

One dimension of the factor analysis of at least consisted of the lowest four questionnaire items, i.e., 3, 4, 5 and 6; the other dimension consisted of the first two items namely 1 and 2. Using the criterion of an eigenvalue of 1.0, the two identified dimensions put together accounted for 63.7% of variability of the original six item variables. All the questionnaire items categorized into the two dimension constructs had communalities greater than 0.518 indicating high internal consistency (Table 4).

DISCUSSION

This study evaluated the knowledge and attitudes of HIV positive patients on ART concerning adverse effects of their antiretroviral medicines following routine adherence counselling and education sessions. Majority of patients presented good knowledge and positive attitudes towards AEs of their medicines irrespective of possible discomfort they were likely to encounter. A few were not very comfortable with the possibility of adverse effects of their medications. Majority of the participants acknowledged that all medicines irrespective of how good they are, still present AEs. Importantly, more than half of these patients reported to know the AEs associated with their particular medicines and also what to do in the event of AEs. A study conducted in South Africa showed good knowledge of ART [11] but this

Table 4. Attitudes towards adverse effects as reported by participants

	Strongly disagree n,%	Disagree n,%	Neutral n,%	Agree n,%	Strongly agree n,%	Rated score means (±SD)	Factor	
							1	2
1."I benefit from my medicines and I get better when I take them" (N=98)	1(1)	0 (0)	0 (0)	9 (9)	88 (90)	4.87 (0.49)	-0.229	0.807
2."Medicines sometimes have adverse effects and can make one's health condition worse" (N=98)	26 (27)	13 (13)	3 (3)	35 (36)	21 (21)	3.12 (1.55)	0.285	0.675
3."It is of no use to ask my doctor or pharmacist about any unpleasant effects of my medicine because knowing will scare me from taking them as instructed" (N=98)	67 (68)	26 (27)	1 (1)	2 (2.0)	2 (2.0)	4.57 (0.80)	0.912	-0.111
4."It is of no use to tell my doctor or pharmacist about my unpleasant experience (side effects) with my medicines because I will end up getting more additional medicines" (N=98)	72 (74)	20 (20)	1 (1)	3 (3)	2 (2)	4.60 (0.83)	0.940	-0.128
5."Adverse effects of my medicines are my problem for which I should worry about and take responsibility" (N=98)	57 (58)	18 (18)	2 (2)	5 (5)	16 (16)	3.97 (1.52)	0.518	0.091
6."I will stop or feel scared to continue my medications if I know that my medicines can cause undesirable/horrible effects when I take them" (N=98)	79 (81)	15 (15)	0 (0)	3 (3)	1 (1)	4.71 (0.72)	0.730	0.170

sharply contrasted with findings by other investigators which reported poor knowledge [9,17]. The study designs were similar to what was employed in this study as knowledge was based on "patients self-report" events. In these studies, it was evident that good knowledge of the AEs of ART supports positive attitudes in patient medication-taking behaviour [9]. All the measured socio-demographic characteristics of the study participants were found not to be associated with knowledge of AEs. This is contrary to a study reported by Agu et al. in 2012 which found that knowledge of AEs was associated with female gender, self-employment status and older age [21]. This might be due to the low numbers in our sample size as compared with the multi-centre approach incorporating over 2329 patients from 36 public hospitals reported by Agu et al. [21]. Out of 98 participants, 80 (82%) were willing to report their AEs to their healthcare provider in the hospital, but 6 (6%) indicated they will take another drug to treat suspected AEs on their own as against 5 (5%) who preferred to relax and do nothing. These results are similar to a KAPS study in Nigeria [21]. Only 2% of the 98 patients were willing to use herbal medicine to resolve AEs of their medicines while one patient preferred to reduce the dose recommended personally. These indicate positive attitudes as the knowledge acquired obviously from the counselling session is preventing them by from doing things their own way, usually supported by common sense beliefs about medicines, which are strongly influenced by subjective experiences of their illness and the innate fear of self-medication. A study by Horne et al. [17] also made similar findings and comments about knowledge and attitudes on the uptake and adherence to ART.

Majority of participants were convinced that they get better when they take their medicines, another positive attitude to drug therapy. An interesting point is an attitude statement like "medicines sometimes have adverse effects and can make one's health condition worse" scoring higher than the midpoint therefore indicating a positive attitude. This indicates that awareness of the likelihood of AEs in reaction to their medications is not seen as a "bad thing" but rather an unavoidable effect of medicine use, which they must adapt to. Patients' experiences resulting from possible lower CD4 count and immune reconstitution syndrome effects, when they initially start ART, lead to severe AEs and this can influence negative attitudes. Previous studies [6,26,27], reported that AEs are often cited as lowering quality of life when the impact of ART is evaluated. However, patients who can adhere to their ART despite the initial discomfort soon experience a better quality of life and develop positive attitude to their medicine [28]. Regarding the rated score means, attitude items like "AEs of my medicines are my problem for which I should worry about and take responsibility" are clearly negative attitudes and scored a low of 3.97 below the midpoint of 4.31, clearly showing a negative tendency. The study reported by Agu et al. [21] had similar scorings below midpoint clearly reflecting negative attitudes. Such demonstrations of negativity is presented by patients who are developing neuroticism to long-term chronic therapy as demonstrated by Johnson et al. [7].

Of additional interest is the factor analysis, which reduced the six variable items of the questionnaire on attitude to 2-factor constructs which in general represented

the components of attitude being reflected from the survey findings and supported the rated score means analysis of the results. The findings indicate that attitude variable items 1 and 2 (numbers stated on the questionnaire items in table 4) carry similar latent attitudinal components as reflected by their scores and appear to lean towards the cognitive aspect of attitude. In other words, these participants will persist in adhering to their medication irrespective of AEs, believing they will get better and experience an improvement in their quality of life. On the other hand, items 3, 4, 5, and 6 carry the other aspects of attitude namely "behavioural and affective." Here, a patient may resign to the fears and emotions associated with AEs of ARVs and may choose not to discuss problems encountered with their healthcare professionals. This group of patients are likely to discontinue ART or may not adhere or comply with ART as expected. These two constructs of attitude resulting from the survey give an indication that although the education and counselling provided at ART initiation appear useful, continuous engagement, monitoring for signs of neuroticism and prompting of patients to report on the AEs they encounter could improve on the general outcomes of ART in PLWHA. This finding is corroborated by a study in Nigeria [29] which found that lack of adherence to ART medications and attrition or discontinuation from health services contribute to poorer health outcomes and waste limited resources. Identifying patient characteristics, which are associated with poorer outcomes, could be used for making evidence-based decisions to improve patient care. The findings of this study consistent with the findings of Agu et al. [21] that HIV patients are well informed about the AEs of their medications and the majority have positive attitudes towards reporting AEs to their health professionals. It also challenges previous studies [30] that argue that patients do not want to know about the AEs of their medicines. It also emphasizes the need for continuous engagement with patients to determine their challenges with AEs and quality of life perceptions. This could help identify attitudes, which could result in additional interventions to prevent treatment attrition, discontinuation, and neuroticism and help improve treatment outcomes.

The adherence counselling and education on the disease and drug therapy provided as part of the clinical care services may have contributed to the better knowledge and positive attitudes of patients, but this survey clearly indicates that continuous education and counselling is necessary to achieve maximum outcomes. Other studies have also shown that patients desire to be told the full AEs of their medications and their attitudes should be continuously assessed to improve treatment outcomes and that health providers should not depend on their discretion alone to choose when and where to inform them [14].

Limitations of this study include the possibility of excluding very sick patients either on admission, defaulters over the period of the study and patients whose relatives refill their medication on proxy grounds. Again, some patients may have exaggerated their responses towards good knowledge attitudes to their medicines to impress the researcher (response bias) which may overestimate the effects being measured in this study. There may also be recall bias when responding to the survey questionnaire leading to the possibility

of overestimating or underestimating the effects measured. The sample size of 98 study participants is also a limitation as it prevents possible generalization of the results to the population of PLWHA in Ghana.

CONCLUSION

In conclusion, most of the patients living with HIV/AIDS who participated in this study were counselled about their disease condition as well as the adverse effects of their antiretroviral medicines. Majority of patients reported good knowledge of, and positive attitudes to the adverse effects of their medicines. Good knowledge of AEs as reported by most patients may have influenced the positive attitudes towards medication taking habits of participants. The adherence counselling and education being provided should be continuous and not at the discretion of health professionals but as part of the clinical care services. The use of factor analysis in determining possible attitudinal traits could also help in determining the possibility of discontinuation of ART due to AEs by patients.

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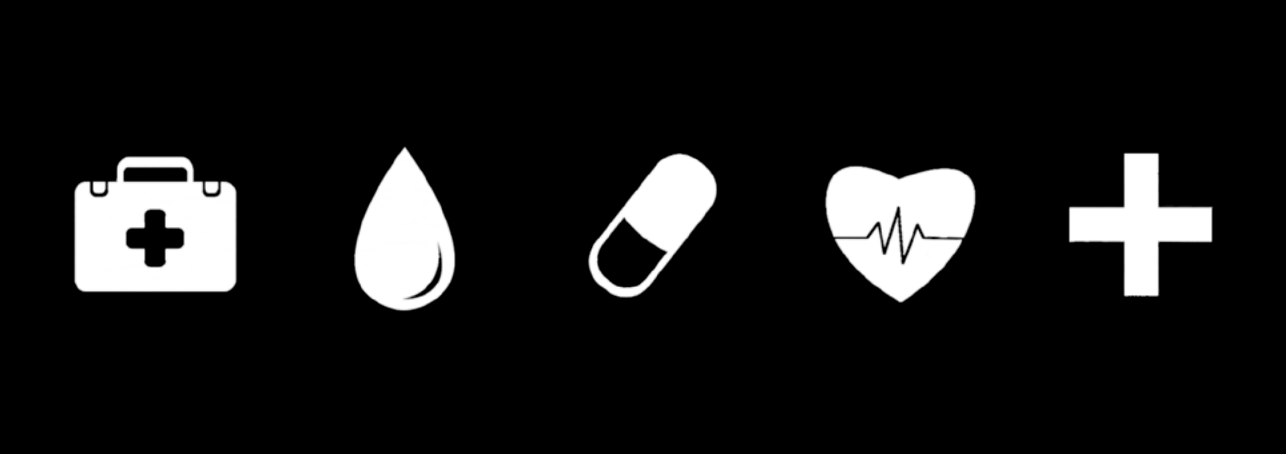

Chapter 4

GENERAL DISCUSSION

SAFETY OF ANTI-RETROVIRAL MEDICINES IN A RESOURCE LIMITED COUNTRY

Considerable experience is available in the developed world with the use of antiretroviral medicines (ARVs). Data generated over time, both in the clinical trial stages as well as post marketing surveillance period, has shown that significant safety issues including adverse reactions are associated with ARVs, both in short and long term usage [1,2]. Specific side effects to ARVs are known from literature and informational inserts that accompany these medicines indicate possible types of adverse drug reactions associated with specific drugs. This situation enables health professionals to advice patients appropriately on the likelihood of adverse events [3].

Limited information about locally documented adverse effects of ARVs are available globally, concerning populations within developing countries [4]. Considering the different circumstances prevailing in developing countries, use of medicines could be affected by different factors and conditions. Therefore, the need to generate local information on the adverse effects of medicines meant for life long usage is very important. Other diseases such as malaria, tuberculosis and worm infestations coupled with traditional beliefs and the practice of alternative medicine pose additional confounding problems that can mask or worsen possible adverse reactions. Some adverse effects may be due to concomitant illnesses, other medications taken simultaneously with ARVs or even manifestations of opportunistic infections as a result of immune reconstitution. These conditions heighten the need for local interpretation of documented data [3].

The absence of comprehensive medicine safety monitoring systems (pharmacovigilance) which not only capture adverse events but incorporates risk evaluation minimization and communication is another shortfall of medicine use systems in resource limited settings such as Ghana [5,6]. Relatively higher illiteracy rate, poor funding of healthcare, poor infrastructure and stigmatization of sexual transmitted diseases creates additional burden for the few qualified doctors, pharmacists and nurses and other healthcare workers [7]. Consequently, explaining adverse reactions reported in books and scientific literature that does not reflect local manifestations can be daunting in the face of other competing practitioners, claiming alternative cures for all diseases without evidence. Africans in general turn to exaggerate events and a misunderstood adverse event can be turned into frightful manifestation that can be rapidly circulated to negatively influence others from initiating the use of ARVs [6].

The need therefore for studying the adverse events associated with use of ARVs in such populations is of paramount importance. The objective of this thesis was to investigate signals of previously unidentified adverse events as well as known signals in patients living with HIV (PLHIV) and that of HIV negative health workers exposed to body fluids of HIV infected patients. Looking ahead, a review of the safety issues associated with the use of ARVs in pre-exposure prophylaxis (PrEP) was also carried out in **Chapter 2.3**, taking into consideration the large numbers of discordant couples in our setting and individuals with risky lifestyle who could be protected from getting infected with HIV through the use of PrEP,

once safety concerns of long term use in our population was established. Another study in **Chapter 3.1** identified risk factors predisposing PLHIV patients to regimen modifications and how these can be prevented. Again, finding out patients' knowledge, attitudes and practices are important resources which can be used to improve healthcare services provided to them so this was investigated in **Chapter 3.3**. Engaging PLHIV patients on therapy after a given period could provide enormous information about knowledge acquired by patients while on ARVs, the influences leading to adherence and non-adherence and how to cope with their lifelong condition. Some ARVs are also associated with specific adverse effects which could be genetically linked or environmentally induced [8]. This requires local monitoring over time to determine the degree or incidence rate of manifestation in different populations.

Two major monitoring methods of pharmacovigilance were deployed in gathering information from PLHIV and HIV negative healthcare workers. Cohort event monitoring was used to gather data from healthcare workers provided with PEP for feedback on adverse effects (AEs) and spontaneous reporting of AEs by patients as captured by doctors and pharmacists in medical and pharmacy notes, when patients present for clinical review sessions [3]. It was anticipated that the findings of these studies would provide evidence based information to guide medicine selection and modification, to minimize adverse effects taking cognizance of the likely incidence rates and predictors of risk factors in our populations, reduce stigmatization and misinformation by providing sound evidence based data to support the use of ARVs [3]. In an expert review of the pharmacovigilance in resource-limited countries by Olsson et al in 2015, it was reported that a "few dedicated healthcare professionals on the field take it upon themselves to introduce a reporting and learning system in their environment with a view to minimize the recurrence of such harms in the future [6]. This thesis therefore presents an example of presenting findings on ARV related toxicity in a typical resource-limited country, i.e. Ghana.

SAFETY FINDINGS AND CONCERNS IN THE USE OF ARVS FOR POST AND PRE EXPOSURE PROPHYLAXIS

The use of antiretroviral drugs for post exposure prophylaxis following occupational exposure to HIV for healthcare workers was recommended as part of the protocol for the management of HIV/AIDS in the Korle Bu Teaching Hospital from 2003 [3] when clinical care services was started for PLHIV. In recent years, its use has been extended to other non-occupational exposures, including unprotected sexual exposure, injecting drug use and exposure following sexual assault [3]. This thesis presented two study outcomes on the use and safety findings in PEP for occupational exposures only. Another study on pre-exposure prophylaxis reviewed landmark safety issues presented in clinical trials and real life usage of ARVs as preventive measure against HIV infection.

Chapter 2.1 provides information on the outcomes of PEP services to Healthcare workers and students. The study observed that 65 health workers considered at high risk of HIV infection using both the rapid assessment system (RAS) and rapid test kit for HIV

infection to confirm did not sero-convert to HIV positive status after the administration of triple therapy of ART for 28 days. This observation is indicative of the usefulness of ARVs. Other reported studies worldwide provided similar results confirming the benefits of PEP services for occupational exposures [9,10]. The availability of such services and the findings of negative HIV sero-conversion in health workers exposed to the body fluids of HIV positive source patients, strengthens the confidence of these workers to overcome the anxiety, stress and fear associated with exposure to body fluids of patients in general.

The RAS was proven to be a very necessary complementary tool in our setting where limited availability of HIV rapid diagnostic test kit at all service points could pose challenging moments in deciding whether to use dual or triple therapy of ARVs in preventing possible HIV infection in an exposed healthcare worker. The study also observed that ward attendants were found to be 4 times at greater risk of getting a needlestick injury requiring PEP than nurses. This was an interesting finding, since this group of healthcare workers hardly come into direct contact with patients. The lack of proper disposal arrangements in most wards of the hospital could explain this finding since in the attempt to remove used syringes with needles; they become exposed to percutaneous injuries. Use of safer medical devices, such as sharps with engineered sharps injury protections and needleless systems is recommended. These same findings and recommendations are made in other studies of note [11,12].

A limitation of the study was the inability to establish the number of healthcare workers who were equally exposed but did not seek PEP services as that could serve as control to really justify the real world benefit of ARVs in PEP use given that the risk of sero-conversion from percutaneous exposure without intervention is 0.3% and 0.09% in mucocutaneous exposures.

Chapter 2.2 presented findings of AEs and adherence to PEP. The study found that adverse events were very common (1 in 10) in exposed healthcare workers on ARVs, irrespective of 3 or 28 days duration of administration. It was also evident that those on triple therapy presented with more AEs than those on dual therapy. It also showed that serious AEs leading to hospitalization were common with a frequency of 1 to 100 (3 cases in 228 healthcare workers) with all three of the female gender and on triple therapy.

The overall AE frequency was 64% compared to 70% and 76% as reported in other similar studies [13,14]. The AEs reported by these healthcare workers were consistent with the product profiles of the ARVs in use. Of note was the finding of dark pigmentation (hyperpigmentation) reported by a patient on 3TC/AZT/LPV/RI for 28 days which another study also mentioned as a cutaneous adverse reaction of zidovudine [15]. A case of spontaneous miscarriage was recorded in a patient in the first trimester of pregnancy. This patient was on category "C" ARVs, same type as mentioned above. This therefore necessitates constant vigilance in the use of these medicines to generate enough evidence to support or preclude their use in pregnancy, especially in the first trimester.

An overall adherence rate of 77% to PEP was determined in the study, a finding similar to some published reports but much higher than what others reported [14,16]. The use of

a cohort event monitoring (CEM) technique in this study led to the successful monitoring of adverse events and adherence to PEP schedules and is highly recommended. The study also demonstrated that it is possible to effectively conduct an active safety monitoring of ARVs used in PEP in resourced limited settings by using mobile telephones to follow up on healthcare workers and solicit their experiences. The study pointed to the importance of focused cohort studies in generating important safety information in resource limited settings where spontaneous reporting of AEs yields very little data in a systematic manner. A possible limitation of this study was the in-house medication adherence metrics used as against a validated tool such as by Morisky et al. [17].

Chapter 2.3 reviewed safety concerns observed in completed clinical trials on the use of PrEP. It also reviewed findings from routine real-life practice reports on the safety of tenofovir disoproxil fumarate in combination with emtricitabine with the trade name of Truvada®. From the clinical trials reviewed, it is evident that PrEP is highly effective against HIV infection when taken as required in at-risk groups. Our review showed a favourable pattern of AEs for PrEP among eligible populations. Some reported side effects with the start of PrEP gradually resolve, and even the more serious listed ones such as increased serum creatinine levels (leading to kidney dysfunction) return to normal after discontinuation of PrEP. The reduction of bone mass density after cessation of tenofovir also returns to normal. The use of tenofovir based PrEP was also not associated with serious hepatic complications, however monitoring of liver enzymes is recommended. A cautionary measure very crucial to PrEP use is the identification of people who are sero converting [18] since it is strictly meant for HIV-negative individuals. PCR screening is recommended to reduce the likelihood of people in the window period of HIV infection starting PrEP as resistant strains may pose problems. Several studies including West African women on tenofovir based PrEP demonstrated a reduction in high risk sexual behaviour with counselling during PrEP [18-20]. Newer agents with better safety profiles may offer advantages, because unwarranted treatment discontinuation due to adverse effects exposes at risk partners to risk of HIV infection. Maraviroc, rilpiverine and carbotegravir under consideration for PrEP have good safety profile in HIV therapy but efficacy and safety is yet to be established in HIV uninfected persons [21]. Another new formulation, tenofovir alafenamide, provides 90% lower plasma levels of tenofovir and has proven to have favourable renal and bone safety profile better than original tenofovir but its efficacy and safety is also yet to be established in HIV negative populations [21].

SAFETY FINDINGS AND CONCERNS IN THE USE OF ARVS IN ANTIRETROVIRAL THERAPY

Antiretroviral medications have proven to be effective in the management of HIV [3,22,23]. The simplicity or complexity of regimens used requires careful monitoring and adherence to therapy to ensure efficacy and prevent resistance. Regular laboratory monitoring after start of ART is necessary to identify side effects, viral suppression and drug resistance [3].

Antiretroviral agents are responsible for a broad range of adverse effects which can result in modification of various regimens [24,25]. Certain risk factors at initiation of ART could predispose patients to adverse reactions leading to unnecessary switches thereby limiting available ARV options for use, especially in resource challenged countries.

In Chapter 3.1, the study investigated the association between AEs and ART modification and then further documented the adverse drug events of HIV positive Ghanaian patients The study finding indicating that a higher proportion of PLHIVs (80.5%) switched from first-line to first line ART regimens than from first-line to second line (19.5%) was similar to other studies in developed countries [26,27]. The median duration of 344.5 days from ART initiation to modification was also comparable to a south Indian and a South African studies of similar nature (406 and 447 days, respectively) [28,29]. These findings indicate that patients generally fared well on most initiating regimen for at least a year before therapy modification, and these modifications could be due to persistent adverse drug events, policy changes or treatment failure. An association was found to be significantly associated with ART modification with odds ratio of 2.71. This was confirmed by other similar studies [24,25]. Furthermore, the proportions of patients experiencing an adverse event before therapy modification in this study was found to be similar to the proportions found in studies in Brazil [30] and Ethiopia [31] at between 56.1 to 53.8%, but another case control study in Ethiopia reported that as many as 85.7% of patients modified therapy because of adverse drug events [32]. Anaemia, nutritional and metabolic disorders and peripheral neuropathy were the most reported adverse events in patients with modified therapy. Anaemia, the most reported AE was mostly from the use of zidovudine, but was totally absent in patients on stavudine. Peripheral neuropathy and metabolic disturbances were mostly documented in stavudine based regimen. These documented adverse reactions are directly associated with the use of these two drugs and other studies confirm causality [33-35].

The presence of drug toxicity or poor medication adherence may limit any derived benefit from ART and often results in therapy modification which can be costly in terms of narrowing regimen options available to patients, posing major challenges to national programs in resource-constrained settings like Ghana. In a study from the same study site evaluating the effect of ART adherence on treatment modification, Ankrah et al. found that after adjusting for confounders, adherence level below 95% was associated with an increased odds of almost four (aOR 3.56 (95%CI 1.66-7.88) of having a treatment modification [36]. The data suggested that the occurrence of AEs contributed to non-adherence. It is therefore prudent in such places to ensure close monitoring of adverse drug events using both clinical and laboratory investigations in order to provide early interventions to mitigate any untoward ART modification [27]. Management of adverse drug events including dose adjustments and the choice of appropriate regimen is a key strategy for improving adherence among PLHIV on therapy [3] and the avoidance of any subsequent therapy modification. This study was limited by the lack of routine baseline viral load determination which could have served to determine treatment failure requiring therapy modification, unavailability of random

resistance testing for baseline determination in failing regimen contributed to inability to determine possible effect of primary resistance to initiating ARVs on our findings. Poor record keeping in most resource settings also served as limitation in retrieving complete data sets on patients.

Chapter 3.2 presented findings on the long term adverse effects of tenofovir based regimen on the renal profile using creatinine clearance as a marker and also determined potential risk factors associated with toxicity. The study determined that 63 patients out of 300 participants on tenofovir contributing 842.8 person years in the cohort experienced significant declines in creatinine clearance over the 5 years period of the study. Out of this number, 7 patients developed severe renal impairment. The factors found to be associated were older age, decreased creatinine clearance at baseline, WHO HIV stages III and IV and baseline body mass index of below 18.5kg/m^2. These findings were comparable to other similar studies [37-40]. Other findings of secondary relevance regarding cohort characteristics, e.g. gender balance, age groups, marriage, religious affiliations and educational levels of participants were similar to most findings in sub-Saharan Africa as reported by WHO [41]. WHO HIV stages III and IV were determined in 57% of patients and this was found to be associated with declining renal performance. Literature supports this finding [42], however with 44% of patients presenting with CD4 below 150cells/mm, this study did not find any association with renal impairment much unlike findings from a south African study which reported an association between CD4<150cells/mm and renal impairment [38,40]. Tenofovir-based regimens are presently recommended as the preferred first-choice therapy in Ghana and in many other African countries where HIV prevalence is relatively high because of its better tolerance, low frequency of adverse events, and compatibility with other drugs resulting in single daily dosing formulations [43]. The question therefore is its long term renal toxicity profile which would require constant laboratory monitoring and which could prove costly in resource limited settings. The use of tenofovir based regimen as preferred first line regimen in Ghana and most African countries is justified by its beneficial attributes, however the incident rate of 7.6 cases per 100 person years as determined in this study supports the need for close monitoring of patients, especially those with these identified risk factors.

Consequently, in **Chapter 3.3,** we evaluated the knowledge and attitudes of patients living with HIV to antiretroviral therapy following routine counselling and education. While acknowledging that ART has been very effective in reducing morbidity and mortality rates whilst also improving the quality of life immensely for longer periods [44,45] the short and long term adverse events associated with ART threaten adherence to therapy and patients on ART develop diverse attitudes. The study found that majority of patients interviewed presented good knowledge and positive attitudes towards the AEs of their medicines irrespective of the possible discomfort they were likely to encounter. More than half of participants in the study reported awareness of the specific side effects associated with their specific regimens. A study in South Africa reported similar results [46] but other

investigators contrasted, reporting poor knowledge of participants [44,47]. These studies employed similar study design and patients "self-reported" AEs. It was evident that good knowledge of the AEs of ART supports positive attitudes in medication-taking behaviour of patients [47]. The use of factor analysis identified 2 underlying dimensions that described participants' attitude towards adverse effects. Questionnaire items 1 and 2 carried similar components towards the cognitive dimension of attitude. This translates to adherence to medication irrespective of AEs, with the belief that patients will get better. Questionnaire items 3 to 6 carried the other dimension of attitude namely behavioural and affective. This translates to a patient resigning to the fears and emotions associated with AEs of ART who may choose not to discuss problems encountered and who is very likely to discontinue ART. These two dimensions of attitude resulting from the study indicate that although education and counselling sessions provided at ART initiation appear useful, continuous engagement, monitoring for signs of worry or fear, and prompting patients to report AEs could improve general outcomes of ART in PLHIVs. A study in Nigeria [48] corroborated these findings by reporting that lack of adherence to ART medications and attrition or discontinuation from health services contribute to poorer health outcomes and waste limited resources. It is therefore important to identify patients who may become non-adherent or default in treatment. Our study findings could help in identifying individuals likely to discontinue ART. The findings of this study were also consistent with the findings of Agu et al [48] that HIV patients are well informed about the AEs of their medications and the majority have positive attitudes towards reporting AEs to their health professionals. It also challenges previous studies [47] that argue that patients do not want to know about the AEs of their medicines. In fact, another study in Ghana by Sabblah et al. [49] confirmed the positive attitude of patients with regards to knowing the AEs of their medicines and being prepared to report to the National Pharmacovigilance Centre. Their motivation is to contribute to drug safety and also to get more information on AEs from experts [49].

Limitations of this study include the possibility of excluding sick patients on admission, defaulters, and proxy pick-ups of patients' medication by monitors. Their responses could have influenced the final outcomes. Again some patients turn to exaggerate their responses towards good knowledge and attitudes to impress the researcher (response bias) leading to overestimation of the measurable effects, and recall bias could also be a factor. Finally, the sample size of 98 participants prevents generalization of the results to the population of PLHIV in Ghana.

ENSURING THE SAFETY OF ANTIRETROVIRAL MEDICINES IN GHANA

Over the past two decades, many low and middle income countries have established national pharmacovigilance (PV) systems, supported by the WHO global PV network. Unfortunately, very few have fully functional systems in place [4-6]. Generation of local evidence on the burden of medicine-related harmful effects on populations is poor, therefore much

is done towards preventing harm to patients. An executive summary report on systems analysis of Ghana's pharmacovigilance readiness indicated that the Ghana National Drug Policy recognizes the need for pharmacovigilance and medicine information services and considers post marketing surveillance and pharmacovigilance as important aspects of medicine registration and selection in Ghana. But no legal support is in place to enforce activities of pharmacovigilance [5].

The report established that a basic structure for pharmacovigilance activities, including a national center, was in place and functioning. Also that it was adequately staffed, has functional information and technology set-ups and collaborates with the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden. However, no budget line, no safety bulletins, no regular training of healthcare workers and no coordinating mechanism operate across all levels of the healthcare structure, namely national, public health programs and healthcare institutions. In addition, PV guidelines and SOPs were inconsistently reported [5,6].

The data used for the studies in this thesis was made possible by a donated database from Family Health International (FHI), somewhere in 2003 when in collaboration with the Ghana Health Service and the Korle Bu Teaching Hospital, service for PLHIV started. An accompanying hardcopy in the form of a medical folder was used by doctors to capture information on patient care. All reports of adverse events reported by patients or laboratory investigations are captured in the folder and later transferred by data officers unto the database. The database is linked to the pharmacy department and as medicines are dispensed, additional data is generated on adherence, pill counts, reported adverse events, possible drug-drug interactions and default rates of patients. These arrangements enabled operational data to be generated during service provision, making it possible to investigate outcomes in patient care.

The same arrangement is not available for investigating pharmacovigilance issues on the management of other disease conditions, especially non-communicable chronic conditions like hypertension and diabetes. Medical folders for capturing data is cumbersome with no electronic support systems to transfer data for research purposes, making retrospective studies difficult in other disease areas. The Food and Drugs Authority (FDA) of Ghana has provided adverse drug reactions recording forms (ADR) for all health institutions and occasional train healthcare professionals is done to facilitate reporting of adverse events. Healthcare workers do not feel compelled to report AEs, so reports are provided only when prompted. In fact, some health professionals even demand motivation or acknowledgement for reporting AEs [49]. Occasionally, active drug information alerts and withdrawn or problem drugs are circulated to all health facilities to create awareness but follow ups are poor and communication generally require improvement.

According to the Strengthening Pharmaceutical Systems report (SPS) [5], the essential elements of Good Pharmacovigilance Practice (GPP) include a stable quality control system and data safety management, assuring absolute quality in operations and safety data

management, good pharmaco-epidemiological research practices, good systematic signal evaluation and assessment, effective communication, documentary reviews, labelling and regulatory actions that respond to infractions [50]. Institutional capacities should be strengthened to support the development, establishment, functioning, and sustainability of a comprehensive medicine safety system.

Appropriate policies and legal frameworks coupled with an enabling environment, i.e. institutional development including community participation, human resources development, and strengthening of managerial systems, are essential components in capacity building. It can also be achieved through applying a four-tier hierarchy of capacity-building needs: structures, systems, and roles; staff and infrastructure; skills; and tools [6]. The way to go for resource limited countries is to pool resources and operate within geographical settings or economic belts to support each other and given that, demographical characteristics compare favourably, research findings can be extrapolated to larger similar populations to secure preventative measures that could improve the incidence of adverse events and improve the quality of lives of people.

The general public should also be educated and motivated to provide spontaneous reporting and most public health programs in resource limited countries now target patients to report any adverse event [51]. A survey on patients reporting of ADRs by Avery et al. [52] justified future promotion of patient reporting in all countries by confirming that such activities have the potential to add value to pharmacovigilance through capturing different types of drugs and reactions much different from those reported by healthcare professionals (HCPs), also generating new signals and describing ADRs in enough details. In another study Matos et al [53] reported that most countries accept ADR reports from patients by an official reporting system different from HCPs, and also through HCPs. They indicated that the reason why some countries procrastinate could be because of financial restrains, lack of enough information or education of patients. Where patients' attitudes were found to be very positive towards reporting of ADRs, authorities are afraid of over-reporting resulting in huge increases in reporting which they may not be able to handle effectively. In Ghana, according to Sabblah et al. [49], patients have a positive attitude and good knowledge on the reporting of ADRs and so by sustaining public awareness campaigns. Prompt acknowledgement of received ADRs and providing feedback could enhance and benefit the pharmacovigilance system significantly.

Pharmacists and pharmacies could also play leadership roles in pharmacovigilance activities by prompting patients they interact with to report AEs and also promoting the patronisation of the ADR forms by other frontline health professionals [53]. The concept of pharmaceutical care has challenged pharmacists, both clinical and community oriented pharmacists, to play a pivotal role in identification, detection, prevention and management of drug-drug interactions, drug-food interactions and ADRs [54]. These activities are carried out in in-patient settings during clinical care reviews, ward rounds and patient medication profiling and management. With the current vast knowledge in drugs and therapeutics,

the enhanced skills in determining medicine related problems and dealing with them has enlarged the operating arena of clinical pharmacists. Their unique interventions in organizing lectures, workshops, group discussions, and activities of Drugs and Therapeutics Committees has made available information about the importance, awareness, preventability and the necessity of reporting ADRs and this has heightened improvement in knowledge, attitude and perception of patients as well as other healthcare professionals [54,55]. The WHO Collaborating Centre for Training and Advocacy in Pharmacovigilance in Accra focuses on pharmacovigilance training of African countries to build capacity, promote advocacy and strengthen ADR reporting. It also trains regulatory authorities in data management for clinical and regulatory affairs. It also hosts, develops and manages a pharmacovigilance toolkit which provides links to WHO publications, learning courses and guidelines [56]. Social media can also be useful for monitoring the safety of medicines through complex computer data mining algorithms which are under development for future possible use [57,58].

4 POLICY IMPLICATIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The policy implications of this thesis follow the two thematic areas covered, (i) protection of healthcare workers during occupational exposures through use of PEP, and preventing HIV infection of sero-discordant couples, gay partners and individuals with risky lifestyle through PrEP and (ii) increasing post marketing surveillance of ARVs in use to enhance safety of ART in Ghana.

Referring specifically to the studies undertaken, **Chapter 2** calls for the documentation of all occupational exposures and efforts must be made to replace traditional syringe and needles with modern self-destructive devices to reduce the risk of needlestick injuries. It is recommended that all newly employed healthcare workers should be vaccinated against hepatitis B/C. In addition, the use of the rapid assessment system is encouraged in the rural settings where availability of the rapid diagnostic kit for confirming source patient's status could pose problems and access to rapid diagnostic kits is thus low. The deployment of an active pharmacovigilance tool like cohort event monitoring via mobile telephony is a positive finding which must be adopted as a policy by the Ministry of Health to increase post-marketing surveillance reports of new and problem associated drugs in use by patients. Since mobile phones have penetrated every home in Ghana, we can follow up on patients and healthcare workers exposed to occupational exposures to solicit adverse events reporting and also to educate, counsel, and encourage adherence to therapy. The review on safety concerns of PrEP advises that PrEP can be used as an intervention to reduce HIV transmission as it appears to have a safe benefit-risk profile in clinical trials. It is recommended for widespread use but adherence monitoring and real-life safety surveillance are critical to its successful use. Considering the increasing numbers of discordant couples, men on men sexual partners and the fact that use of PrEP is approved for use in advanced countries, policy initiatives should consider its use in the country in the near future.

The studies in **Chapter 3** advise that in the initiation of ART, determined baseline characteristics of patients (weight, abnormal laboratory findings, manifesting signs and symptoms) should be monitored carefully since they are predictors of possible unnecessary treatment modifications, which could reduce our treatment options in time. Standardized protocols for identifying and monitoring adverse drug reactions of antiretroviral medicines should be established to improve the recognition, management and prevention of AEs attributable to ART. Specifically in the use of tenofovir based regimen, it is advised that patients with the identified risk factors for possible renal damage in the study should be targeted and supported to access laboratory investigation despite the limited resources of specific settings (urban or rural) irrespective of the policy to initiate without compulsory baseline laboratory investigations. Finally, the concluding study advises that adherence counselling and education of PLHIV be considered as a continuous activity and should not be at the discretion of healthcare professionals. Constant engagements with patients results in good knowledge of their medications and associated AEs and influences the development of positive attitudes.

A multi-centred cohort study on the outcomes and tolerance of ARV use in PEP services nationwide should be undertaken to obtain a national picture to serve as a guide in developing a national policy on occupational exposures to body fluids and the AEs associated with the use of ARVs in PEP. The small sample size of 298 exposed healthcare professionals is not significant enough to serve as basis for extrapolating the findings of our study on PEP services. Another proposal is for a national determination of the incidence of renal toxicity amongst Ghanaians as a precursor to rolling out the 90/90/90 policy initiative since that could determine the risk to Ghanaians of initiating PLHIV with the preferred tenofovir based regimen without laboratory investigations. Finally, another suggested study could be finding out the knowledge, attitudes and perceptions of healthcare professionals towards patients reporting of ADRs. This could stimulate HCPs to prompt spontaneous reporting from patients resulting in significant increase in AEs reportage in Ghana.

CONCLUSION

This thesis has determined that AEs to PEP are very common and could be severe requiring hospital management. The need therefore to follow-up on all healthcare workers who receive ARVs as PEP is important. CEM, an active pharmacovigilance tool using mobile phones, could be deployed in following up all patients on ART to solicit AEs and to advice on management. PrEP as an intervention to reduce HIV transmission is effective with a safe benefit-risk profile in clinical trials. Real world use is encouraged with the necessary precautions of post marketing surveillance, behavioural counselling and assurance of safety and efficacy. The studies in this thesis revealed that adverse events play a major role in PLHIV on ART, resulting in treatment modifications. Monitoring and managing these adverse drug events may help to avoid therapy modification which can result in reducing available treatment options in resource-limited settings. The use of tenofovir based regimen as preferred first

line ART option in Ghana is justified by its beneficial attributes, but patients at higher risk of renal damage should be supported to access laboratory investigation irrespective of the "Treat All Policy". The adherence counselling provided to patients at initiation of ART improves the knowledge of patients and results in positive attitudes leading to enhanced adherence to ART and therefore better outcomes.

Looking ahead, Ghanaian healthcare professionals should collaborate with regulatory bodies (the Food and Drugs Authority, the Ghana Standards Authority), the WHO Collaborating Centre for Training and Advocacy in Pharmacovigilance, the agencies of the Ministry of Health namely the Pharmacy Council, The Medical and Dental Council, The Nurses and Midwives Council and the Allied Healthcare Professionals Board to bring awareness of pharmacovigilance to the frontline of health policy formulation and implementation in order to secure the safety of patients in the use of antiretroviral medicines and also to generate information on these medicines in use to enrich the knowledge of the world community.

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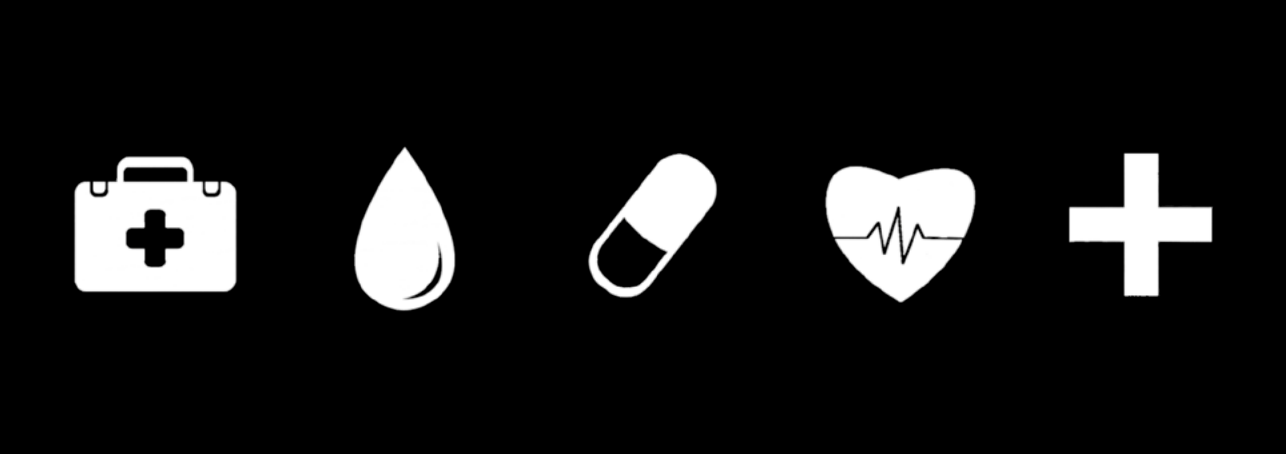
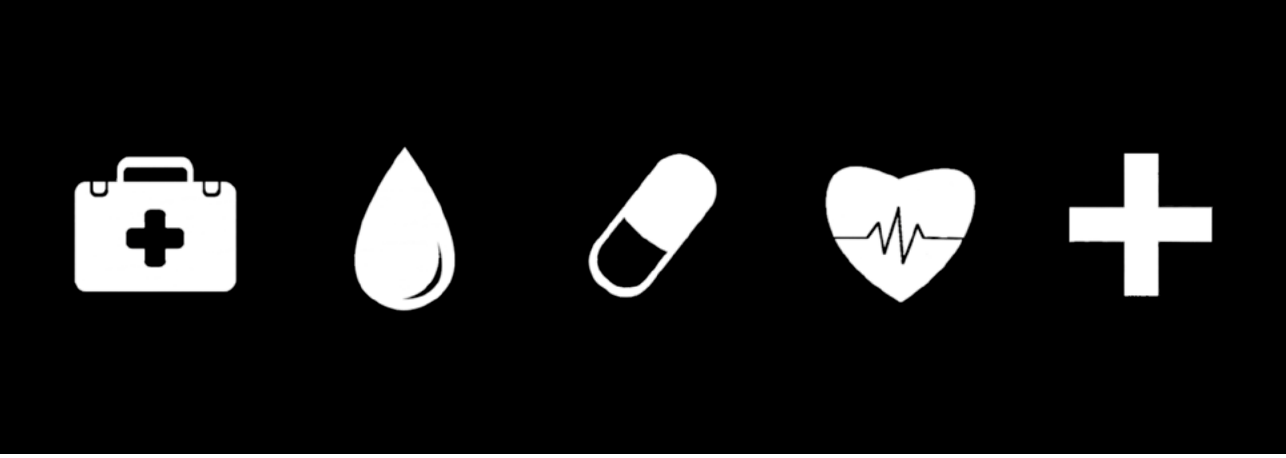


Chapter 5

SUMMARY



Chapter 5.1

SUMMARY

SUMMARY

HIV/AIDS is presently classified as a pandemic event with an estimated 33.2 million people living with the disease. To date over 4 million persons worldwide have died from HIV/AIDS related outcomes including over 600,000 children. More than three-quarters of these deaths occurred in sub-Saharan Africa, destroying human capital while retarding economic growth. Ghana is classified as having a generalised HIV epidemic with HIV prevalence hovering around 2% in the last decade. The WHO further estimates that 3 million percutaneous exposures occur annually among 35 million healthcare workers (HCWs) worldwide, representing 12% of the working population.

Recent reports from UNAIDS indicate the scales are tipping and for the first time more than half of all the people living with HIV/AIDS (PLHIV) (53%) now have access to HIV treatment. Consequently, AIDS related deaths have almost halved since 2005. In Ghana, the National HIV Prevalence and AIDS Estimates Reports for 2011 to 2016 show the national HIV response is making good progress with 89,113 people on antiretroviral therapy (ART) by the end of 2015. The Korle Bu Teaching Hospital (KBTH) in Accra, Ghana alone documented over 400 of percutaneous exposure incidents from 2003 to 2016. Antiretrovirals (ARVs) are also indicated in these cases for post-exposure prophylaxis (PEP).

Much as ART has proven over time to be beneficial and lifesaving, ARVs are responsible for a broad range of adverse effects from low grade self-limiting to life threatening side effects. Adverse effects to ARVs used in ART can lead to treatment cessation or poor adherence resulting in poor treatment outcomes**.** This thesis investigated the use and safety outcomes of ARVs in exposed healthcare professionals and PLHIV.

The thesis looked at two components of the HIV clinical services in KBTH, namely provision of post and pre-exposure prophylaxis and the ART services for PLHIV. The aim was first to investigate the use and safety of ARVs in post exposure prophylaxis for healthcare workers exposed to body fluids of PLHIV and safety of pre-exposure prophylaxis (PrEP), and secondly to investigate the pharmacovigilance of ARVs use in PLHIV. The objectives were to document outcomes and adverse events of PEP in Ghana, discuss the safety concerns of PrEP as observed in clinical trials, document adverse events associated with ART, its effects on treatment modifications and evaluate the knowledge and attitudes of PLHIV to ARVs in Ghana.

The thesis is organized into four main chapters. **Chapter 1** is introductory and provides a general overview of the research topic, the aim and objectives of the research work. The subsequent chapters are summarized as follows;

Chapter 2 focuses on occupational exposures to HIV infection by healthcare workers, the use of anti-retrovirals as post-exposure prophylaxis and the associated adverse events, and safety of pre-exposure prophylaxis. **Chapter 2.1** studied the risk for occupational exposure to HIV as a serious public health problem that is well characterized in the developed world, but less so in developing countries such as Ghana. The study was undertaken to examine the characteristics of occupational exposure to HIV and the utilization of a risk

assessment system (RAS)–based PEP among health care workers (HCWs) and health care students (HCSs) in the Korle-Bu Teaching Hospital (KBTH). During the study period (January 2005–December 2010), a total of 260 and 35 exposures were reported by HCWs and HCSs, respectively. Ward attendants reported the highest incidence rate of 6.46 of 100 person-years (P-Y). The incidence of high-risk exposures was 0.33 of 100 P-Y (n=65); 60.0% occurred during a procedure of disposing of a needle and 24.6% during a cannula insertion. A total of 289 of the 295 individuals were administered PEP, of which 181 (62.6%) completed the 6-month follow-up testing schedule and none sero-converted. This shows that with a good RAS in place, it is possible to deploy an effective PEP program in a typical African teaching hospital like the KBTH in Accra, Ghana.

The side effects of ARVs used as PEP in HIV negative HCWs is not well documented. Following the introduction of a HIV post-exposure prophylaxis program in the Korle-Bu Teaching Hospital in January 2003, the incidence of adverse events and adherence to ARVs in the PEP were documented in occupationally-exposed HCWs and HCSs, as outlined in **Chapter 2.2**. Cohort event monitoring was used in following-up on exposed HCWs/HCSs for the two study outcomes; adverse events and adherence. All adverse events reported were grouped by MedDRA system organ classification and then by preferred term according to prophylaxis regimen. Adherence was determined by the completion of prophylaxis schedule. Cox proportional regression analysis was applied to determine the factors associated with the cohort study outcomes. A total of 228 exposed HCWs/HCSs were followed up during the study, made up of 101 exposed HCWs/ HCSs administered lamivudine/zidovudine (3TC/AZT) for 3 days; 75 exposed HCWs/HCSs administered lamivudine/ zidovudine (3TC/AZT) for 28 days; and 52 exposed HCWs/HCSs administered lamivudine/zidovudine/lopinavir-ritonavir (3TC/AZT/LPV-RTV) for 28 days. The frequency of adverse events was 28 % (n = 28) in exposed HCWs/HCSs administered 3TC/AZT for 3 days, 91 % (n = 68) in exposed HCWs/HCSs administered 3TC/AZT for 28 days and 96 % (n = 50) in exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28 days. Nausea was the most commonly reported adverse events in all three regimens. Adherence was complete in all exposed HCWs/HCSs administered 3TC/AZT for 3days, 56 % (n = 42) in exposed HCWs/HCSs administered 3TC/AZT for 28 days and 62 % (n = 32) in exposed HCWs/HCSs administered 3TC/AZT/LPV-RTV for 28 days. In the Cox regression multi-variate analysis, exposed HCWs/HCSs administered 3TC/AZT for 3 days were 70 % less likely to report adverse events compared with exposed HCWs/HCSs administered 3TC/AZT for 28 days (adjusted hazard ratio (HR) = 0.30 [95 % confidence interval (CI), 0.18-0.48], $p < 0.001$). Exposed HCWs/HCSs administered 3TC/AZT for 3 days were 75 % more likely to adhere to the schedule compared with exposed HCWs/HCSs administered 3TC/AZT for 28 days (adjusted HR = 1.75 [95 % CI, 1.16-2.66], $p = 0.008$).

The intolerance to adverse events was cited as the sole reason for truncating PEP, thereby indicating the need for adequate, appropriate and effective counselling, education, active follow-up (possibly through mobile/phone contact) and management of adverse events. Education on the need to complete PEP schedule (especially for exposed HCWs/HCSs on

28-day schedule) can lead to increased adherence, which is very critical in minimizing the risk of HIV sero-conversion. The present results also indicate that cohort event monitoring could be an effective pharmacovigilance tool in monitoring adverse events in exposed HCWs/HCSs on HIV post-exposure prophylaxis.

In Chapter 2.3, we discussed the safety concerns observed in completed clinical trials on the use of PrEP and also reviewed findings from routine real-life practice reports. We performed a literature search on PrEP in PubMed, the global advocacy for HIV prevention (Aids Vaccine Advocacy Coalition) database, a clinical trials registry (http://www.clinicaltrials.gov) and Google scholar using combination search terms 'pre-exposure prophylaxis', 'safety concerns in the use of pre-exposure prophylaxis', 'truvada use as PrEP', 'guidelines for PrEP use', 'HIV pre-exposure prophylaxis' and 'tenofovir' to identify clinical trials and literature on PrEP. We presented findings associated with safety issues on the use of PrEP based on a review of 11 clinical trials on PrEP with results on safety and efficacy as at April 2016 and also from routine real-life practice reports. The pharmacological intervention for PrEP was tenofovir disoproxil fumarate/emtricitabine in a combined form as Truvada® or tenofovir as a single entity. The main adverse effects observed with PrEP are GI related and graded below 2 for severity. These are basically mild to moderate nausea, vomiting and diarrhea. Major concerns are renal, hepatic and bone toxicity, but these are transient and non-progressive and quickly resolve after discontinuation of TDF. Overall, the benefit-risk profiles of the products used for PrEP appear favourable. It is recommended for widespread use but adherence monitoring and real-world safety surveillance are critical in the post-marketing phase to ensure that the benefits observed in clinical trials are maintained in real-world use.

In **Chapter 3** the focus was on several important aspects of pharmacovigilance of ARVs. Modifications in the HAART regimen may become necessary for a number of reasons including possible acute or chronic toxicities. The study in **Chapter 3.1** therefore documented adverse drug events of HIV-positive Ghanaian patients with HAART modifications and investigated the association between documented adverse drug events and HAART modification using an unmatched case–control study design. This study was conducted in the Fevers Unit of the Korle Bu Teaching Hospital and involved patients who attended the HIV Care Clinic between January 2004 and December 2009 and had been on treatment for at least 1 month before the end of study. Data from 298 modified therapy patients (cases) were compared with 298 continuing therapy patients (controls). Controls were sampled from the same database of a cohort of HIV-positive patients on HAART, at the time a case occurred, in terms of treatment initiation ±1 month. Data were obtained from patients' clinical folders and the HIV clinic database linked to the pharmacy database. The nature of the documented adverse drug events of the cases was described and the association between the documented adverse drug events and HAART modification was determined by logistic regression with reported odds ratios (ORs) and their 95 % CIs.

Among the 298 modified therapy patients sampled in this study, 52.7 % (n=157) of them had at least one documented adverse drug event whilst in the control group, only

4% (n=12) had adverse drug events documented. The most documented adverse drug event was anaemia, recorded in 18.5 % of modified therapy patients, all of whom were on a zidovudine-based regimen. The presence of documented adverse drug events was significantly associated with HAART modification [adjusted OR = 2.71 (95 % CI 2.11–3.48), p=0.001]. Among HIV patients on HAART, adverse drug events (ADEs) play a major role in treatment modification. Occurrence of adverse drug events may be used as a predictor for possible therapy modification. We recommend the institution of active pharmacovigilance in HIV treatment programmes as it permits the proper identification and characterisation of drug-related adverse events. This can help develop approaches towards their management and also to prevent or explain needful therapy modifications.

In **Chapter 3.2** we considered the association of tenofovir (TDF) and renal dysfunction which has remained an area of interest. The purpose of this study was to estimate the long term effects of TDF on renal profile and identify potential risk factors associated with renal impairment in Ghana. We selected 300 consecutive HIV-positive patients (with baseline creatinine clearance above 50 mL/min) initiated on TDF-based antiretroviral therapy (ART) in 2008 from a database capturing all patients on ART at the Korle-Bu Teaching Hospital. Socio-demographic details, clinical characteristics, laboratory and antiretroviral regimen were collected from patients' medical records. Absolute change in creatinine clearance (CrCl) using the Cockcroft-Gault equation was calculated at baseline and at as and when deemed necessary for monitoring by the clinician as per institutional guidelines for renal function test. Renal impairment was defined as a reduction in CrCl to values between 30 mL/min and 49.9 mL/min (moderate renal impairment) and below 30mL/min (severe renal impairment). Cumulative incidence rates for moderate and severe renal impairment were calculated. Relative risks and 95% confidence intervals (CIs) were calculated for factors associated with renal impairment.

Females were dominant (n=213, 71.1%) and the mean age of study participants was 39.1 ± 11.1 years. The median CrCl rate at initiation of TDF-containing ART was 76.8 mL/min. At study endpoint, 63 participants (21.0%) recorded CrCl rate below 50ml/min indicating incident renal impairment, made up of 18.3% moderate renal impairment and 2.3% severe renal impairment. Factors associated with the incidence of renal impairment were increasing age (relative risk ratio (RR)=1.04 [95% CI, 1.03-1.06]) per year, decreasing (per every 1 ml decrease) creatinine clearance rate (RR=1.05 [95% CI, 1.04-1.08]), WHO HIV stage III (RR=3.78 [95% CI, 1.42-10.06]) or Stage IV (RR=3.42 [95% CI, 1.16-10.09]) compared with stage I and participants with BMI of <18.5kg/m^2 underweight (RR=3.87 [95% CI, 2.49-6.03]) compared with patients with BMI of >18.5-24.9 kg/m^2 (normal weight). Patients with these identified risk factors should be targeted and monitored effectively to prevent renal injury.

Finally, in **Chapter 3.3,** we evaluated the knowledge and attitudes of patients to ART following routine adherence counselling and education in the Korle Bu Teaching Hospital in Accra, Ghana. This cross-sectional study was conducted by administering a questionnaire on socio-demographics, knowledge of ADEs of antiretrovirals and attitude to ADEs to

98 patients who were on antiretroviral therapy. A 3-point Likert-scale was used to assess knowledge of ADEs of ART and a 5 point Likert-scale to assess attitudes to ADEs. Mean rated scores for attitude to ADEs were estimated and factor analysis was used to reduce the dimensions of the attitudes observed to identify relevant latent constructs. Sixty-one percent of participants were females and most of the participants were aged 35-44 years (35%). Ninety-nine percent of participants answered that they had been counselled on unpleasant effects of their medicines and 93% knew that all medicines could cause some unpleasant effects. Concerning attitude, 90% of study participants strongly agreed that they benefit from their medicines and get better taking them (mean rated score=4.87 ± 0.49) whilst 27% strongly agreed that medicines may have side effects (mean rated score=3.12 ± 1.55). Majority of the study participants (74%) strongly disagreed that there was no need to tell their doctor/pharmacist about ADEs to antiretrovirals (mean rated score=4.60 ± 0.83). Factor analysis yielded two underlying dimensions (cognitive and behavioural/affective aspects) that described participants' attitude towards AEs. Study participants rating for participants' knowledge on AEs was good and exhibited positive attitudes to AEs of ART. Adherence counselling and education provided to PLHIV before initiation of antiretroviral therapy is beneficial and should be continued.

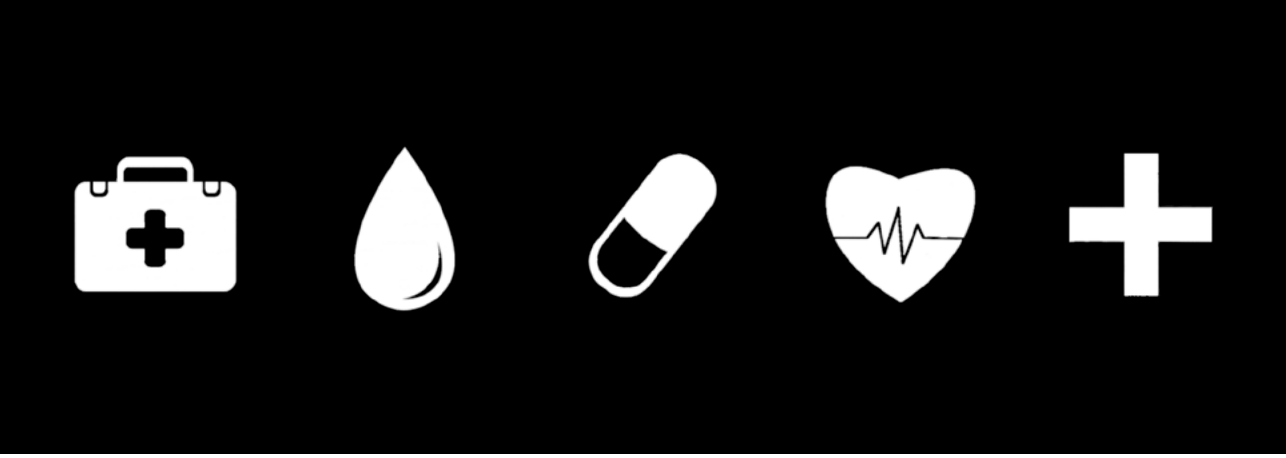
Chapter 4 is the general discussion and concluding chapter of the thesis. Here, the benefits of the use and safety associated with ARVs in general are presented. Health workers at high risk of HIV infection following occupational exposure, can benefit from rapid assessment system (RAS). This has proven to be a complementary tool in settings where limited availability of HIV rapid diagnostic test kit pertains. Similarly, focused cohort studies (cohort event monitoring, CEM) are considered very important in generating important safety information in resource limited settings where spontaneous reporting of AEs yield very little data in a systematic manner. Close monitoring of adverse events is required in resource-constrained settings like Ghana to prevent possibility of regimen switching. Management of adverse drug events including dose adjustments and the choice of appropriate regimen is a key strategy for improving adherence among PLHIV on therapy and the avoidance of any subsequent therapy modifications. Shortfalls in laboratory logistics, human resource capability and lack of reagents result in challenging situations like the inconsistent monitoring of tenofovir based regimens as presented in the TDF study. More efforts are required to prioritize laboratory monitoring of clinical profiles of PLHIV. Additionally, although education and counselling sessions provided at ART initiation appear useful continuous engagement, monitoring for signs of worry or fear, and prompting patients to report AEs could improve general outcomes of ART in PLHIVs.

Over the past two decades, many low and middle income countries have established national pharmacovigilance (PV) systems, but unfortunately very few have fully functional systems in place. Institutional capacities should be strengthened to support the development, establishment, functioning, and sustainability of a comprehensive medicine safety system. The general public should also be educated and motivated to provide spontaneous

reporting. Pharmacists and pharmacies could also play leadership roles in pharmacovigilance activities by prompting patients they interact with to report ADEs and also promoting the patronisation of the ADR forms by other frontline health professionals. Social media can also be useful for monitoring the safety of medicines.

In conclusion, this thesis added to our understanding of the use and safety of antiretroviral medicines in Ghana, as pre- and post-exposure prophylaxis and as part of highly active antiretroviral therapy. Looking ahead, collaboration between stakeholders is necessary to bring awareness of pharmacovigilance to the frontline of health policy formulation and implementation in order to secure the safety of patients in the use of antiretroviral medicines and also to generate information on these medicines in use to enrich the knowledge of the world community.

5.1



Chapter 5.2

SAMENVATTING

SAMENVATTING

Hiv/aids is een wereldwijde pandemie waaraan 33,2 miljoen mensen lijden. Tot op heden zijn 4 miljoen mensen aan de gevolgen overleden, waaronder 600.000 kinderen. Meer dan driekwart van deze sterfgevallen trad op in Afrika ten zuiden van de Sahara. In Ghana lag de prevalentie in het laatste decennium rond de 2%. De Wereldgezondheidsorganisatie (WHO) schat daarnaast in dat de 35 miljoen medewerkers in de gezondheidszorg, 12% van de werkende bevolking, jaarlijks 3 miljoen keer via de huid in contact komen met door bloed overgedragen hiv.

Recente rapporten van UNAIDS laten een kantelend beeld zien; voor het eerst heeft meer dan de helft (53%) van de mensen die lijden aan hiv/aids toegang tot een behandeling. De mortaliteit ten gevolge van aids is daardoor sinds 2005 gehalveerd. In Ghana blijkt uit de 'National HIV Prevalence and AIDS Estimates' rapporten uit 2011 en 2016 dat het nationale beleid zijn vruchten afwerpt en eind 2015 kregen 89.113 mensen antiretrovirale therapie. In het Korle Bu Teaching Hospital (KBTH) in Accra, Ghana werden in de periode 2003-2016 400 incidenten gemeld van mensen die via de huid mogelijk in contact zijn gekomen met hiv. Antiretrovirale geneesmiddelen zijn dan geïndiceerd als postexpositieprofylaxe (PEP).

Hoewel antiretrovirale therapie bewezen effectief is, veroorzaken antiretrovirale middelen een breed scala aan bijwerkingen. Deze variëren van mild en van voorbijgaande aard tot levensbedreigend. Bijwerkingen kunnen daarbij leiden tot staken van de therapie of slechte therapietrouw, wat de effectiviteit van deze middelen negatief beïnvloedt. In dit proefschrift zijn twee aspecten van het gebruik en de veiligheid van antiretrovirale middelen in het KBTH onderzocht, namelijk pre- en postexpositieprofylaxe en farmacovigilantie van antiretrovirale middelen bij patiënten met hiv/aids. Het doel was ten eerste de uitkomsten en bijwerkingen van PEP in Ghana te beschrijven, ten tweede de veiligheid van pre-expositieprofylaxe (PrEP) zoals die wordt gezien in klinische onderzoek te bespreken en tenslotte de bijwerkingen van antiretrovirale middelen bij patiënten met hiv/aids te onderzoeken, waarbij ook het effect op veranderingen in de therapie en de kennis en houding van patiënten ten aanzien van deze middelen is bestudeerd.

Dit proefschrift bestaat uit vier delen. Hoofdstuk 1 vormt de introductie en geeft een algemeen overzicht van het onderwerp en de doelen van het onderzoek. Hoofdstuk 2 richt zich op het via de huid in contact komen met door bloed overgedragen hiv door gezondheidsmedewerkers, het gebruik en de bijwerkingen van antiretrovirale middelen als PEP en de veiligheid van PrEP. Het in hoofdstuk 2.1 bestudeerde gezondheidsprobleem van het via de huid in contact komen met door bloed overgedragen hiv door gezondheidsmedewerkers is goed gedocumenteerd voor ontwikkelde landen, maar niet in Ghana. In dit onderzoek werden de karakteristieken van blootstelling en het gebruik van een risicobeoordelingssysteem bij gezondheidsmedewerkers en (para)medische studenten in het KBTH onderzocht. Gedurende de onderzoeksperiode van januari 2005 tot en met december 2010 waren 260 medewerkers en 35 studenten blootgesteld. De hoogste incidentie, 6,46 blootstellingen per 100 persoonsjaren, werd gevonden voor zaalmedewerkers.

De incidentie van hoog-risico blootstellingen was 0,33 per 100 persoonsjaren (n=65); 60,0% gebeurde tijdens het weggooien van een naald en 24,6% bij het inbrengen van een canule. Van de 295 blootgestelde personen kregen 289 PEP en daarvan ondergingen 181 (62,6%) in de daaropvolgende 6 maanden alle voorgeschreven testen. Er vond geen seroconversie plaats. Deze resultaten laten zien dat het met een goed risicobeoordelingssysteem mogelijk is om in een typisch Afrikaanse ziekenhuissetting, zoals het KBTH in Accra, een effectief PEP programma op te zetten.

Er is weinig bekend over de bijwerkingen van antiretrovirale geneesmiddelen als PEP bij hiv- negatieve gezondheidswerkers. Na de introductie van een PEP programma in het KBTH in 2013 werden in het onderzoek zoals beschreven in hoofdstuk 2.2 de incidentie van bijwerkingen van antiretrovirale middelen en de therapietrouw bestudeerd. Door middel van cohort event monitoring werden deze uitkomsten onder gezondheidswerkers en studenten die PEP kregen onderzocht. Alle bijwerkingen werden volgens het MedDRA systeem op het niveau van de preferred term geclassificeerd en per profylaxeregime geanalyseerd. Therapietrouw werd vastgesteld aan de hand van het voltooien van het innameschema. Een Cox proportional hazard regressieanalyse werd gebruikt om factoren te identificeren die samenhingen met de uitkomsten. In totaal werden 228 gezondheidswerkers of studenten gevolgd, van wie 101 waren blootgesteld aan lamivudine/zidovudine (3TC/AZT) gedurende 3 dagen, 75 aan 3TC/AZT gedurende 28 dagen en 52 aan lamivudine/zidovudine/lopinavir-ritonavir (3TC/AZT/LPV-RTV) gedurende 28 dagen. Van de mensen die 3 dagen 3TC/AZT kregen, kreeg 28% (n=28) een bijwerking. Deze percentages waren 91% (n=68) bij mensen die 28 dagen 3TC/AZT kregen en 96% (n=50) bij mensen die 28 dagen 3TC/AZT/LPV-RTV ontvingen. Misselijkheid was bij alle drie de regimes de meest gerapporteerde bijwerking. Therapietrouw was volledig bij alle mensen die 3 dagen 3TC/AZT kregen, bij 56% (n=42) van de mensen die 28 dagen 3TC/AZT kregen en bij 62% (n=32) mensen die 28 dagen 3TC/AZT/LPV-RTV ontvingen. Uit de multivariate Cox regressieanalyse bleek dat mensen die 3 dagen 3TC/AZT gebruikten 70% minder kans hadden om een bijwerking te rapporteren dan mensen die deze combinatie gedurende 28 dagen gebruikten (gecorrigeerde hazard ratio (HR)=0.30 [95% betrouwbaarheidsinterval (BI), 0.18-0.48], p<0.001). Ook hadden zij een 75% grotere kans om therapietrouw te zijn (gecorrigeerde HR=1.75 [95 % BI, 1.16-2.66], p=0.008).

Bijwerkingen waren de enige reden om PEP af te breken. Dit onderstreept de noodzaak voor adequate voorlichting, actieve bewaking (mogelijk via telefonisch contact) en een goede behandeling van bijwerkingen. Voorlichting over het belang van het afmaken van het PEP schema kan, vooral bij de 28-daagse regimes, tot betere therapietrouw leiden en zo het risico op hiv-seroconversie verminderen. Dit onderzoek laat ook zien dat cohort event monitoring een effectieve manier is om bijwerkingen bij dit soort behandelingen onder gezondheidswerkers en studenten in kaart te brengen.

In hoofdstuk 2.3 wordt de veiligheid van PrEP beschreven zoals die is waargenomen in afgerond klinisch onderzoek en de dagelijkse klinische praktijk. We hebben daartoe in april 2016 een literatuuronderzoek gedaan in PubMed, de 'Global advocacy for HIV prevention

(Aids Vaccine Advocacy Coalition) database', een register van klinische studies (http://www.clinicaltrials.gov) en Google scholar. Een combinatie van de zoektermen 'pre-exposure prophylaxis', 'safety concerns in the use of pre-exposure prophylaxis', 'truvada use as PrEP', 'guidelines for PrEP use', 'HIV pre-exposure prophylaxis' en 'tenofovir' werd gebruikt om studies naar PrEP te identificeren. Gegevens over de veiligheid en effectiviteit van PrEP werden gevonden in 11 klinische studies en rapporten uit de dagelijkse klinische praktijk. PrEP bestond uit het combinatiepreparaat tenofovirfumaraat/emtricitabine (Truvada®) of tenofovir als monotherapie. De voornaamste bijwerkingen betroffen het maagdarmkanaal en werden qua ernst geclassificeerd als klasse 2. Het ging met name om milde tot matig-ernstige misselijkheid, braken en diarree. Ernstigere bijwerkingen betroffen nier-, lever- en beenmergtoxiciteit, maar deze zijn niet-progressief en van voorbijgaande aard. Deze bijwerkingen verdwijnen na staken van de therapie. Het baten-risicoprofiel van de middelen die voor PrEP worden gebruikt lijkt gunstig. Gebruik op grote schaal wordt daarom aangeraden, maar bewaken van therapietrouw en de veiligheid in de klinische praktijk in de postmarketing fase zijn van cruciaal belang om te borgen dat de gunstige effecten zoals die werden gezien in het klinische onderzoek daadwerkelijk worden behaald.

In hoofdstuk 3 richtten we ons op een aantal belangrijke aspecten van farmacovigilantie van antiretrovirale geneesmiddelen. Modificaties van highly active (krachtige) antiretrovirale therapie (HAART) kunnen om verscheidene redenen noodzakelijk zijn, waaronder acute of chronische bijwerkingen. In het onderzoek in hoofdstuk 3.1 is daarom bestudeerd welke bijwerkingen optraden bij Ghanese HIV-patiënten die een aanpassing van hun HAART hadden. Tevens werd de associatie tussen het optreden van bijwerkingen en aanpassingen van de therapie geanalyseerd in een ongematcht patiënt-controleonderzoek. Dit onderzoek werd uitgevoerd onder patiënten die de 'HIV Care Clinic' van de 'Fevers Unit' van het KBTH bezochten in de periode januari 2004 tot december 2009 en die tot het einde van het onderzoek tenminste gedurende 1 maand HAART hadden ontvangen. Gegevens van 298 patiënten van wie de behandeling was aangepast (cases) werden vergeleken met gegevens van patiënten zonder aanpassingen in hun medicatie (controles). Controles kwamen uit hetzelfde cohort als de cases, hadden op dat moment geen aanpassing in de therapie en waren op hetzelfde moment (±1 maand) gestart met de behandeling als de betreffende case. Gegevens waren afkomstig uit de klinische statussen van de patiënten en de gekoppelde databases van de kliniek en de apotheek. De associatie tussen het optreden van bijwerkingen en modificatie van de HAART werd geanalyseerd met behulp van logistische regressie waarbij odds ratio's (ORs) en 95% BIs werden berekend.

Van de 298 patiënten met een aanpassing in de therapie kreeg 52,7% (n=157) tenminste 1 bijwerking, terwijl dit slechts in 4,0% (n=12) van de controlegroep het geval was. De meest gerapporteerde bijwerking, die voorkwam bij 18,5% van de patiënten met een aanpassing in de medicatie, was anemie. Deze patiënten gebruikten allemaal een behandelregime met zidovudine. Het optreden van bijwerkingen was statistisch significant geassocieerd met een wijziging in de HAART [gecorrigeerde OR=2,71 (95 %

BI 2,11–3,48), p=0,001]. Bijwerkingen spelen dus een belangrijke rol bij het optreden van wijzigingen in de therapie en hebben mogelijk een voorspellende waarde in dezen. Actieve farmacovigilantie binnen hiv-programma's wordt daarom aangeraden. Goede identificatie en karakterisering van bijwerkingen in zulke programma's kan tevens bijdragen aan het ontwikkelen van strategieën om deze bijwerkingen te beheersen en aanpassingen in de therapie te voorkomen of verklaren.

In hoofdstuk 3.2 hebben we de associatie tussen tenofovir (TDF) en renale dysfunctie bestudeerd. Het doel van dit onderzoek was het schatten van de langetermijneffecten van TDF op de nierfunctie en het identificeren van mogelijke risicofactoren voor renale insufficiëntie in Ghana. Hiertoe werden aselect 300 hiv-positieve patiënten geselecteerd die startten met TDF als onderdeel van hun antiretrovirale therapie in 2008 in het KBTH. Bij aanvang van de behandeling moesten zij een creatinineklaring (CrCl) boven de 50 ml/min hebben. Sociaal-demografische, klinische en laboratoriumgegevens waren net als gegevens over de behandeling afkomstig uit een database met medische gegevens over de patiënten. De absolute verandering in CrCl ten opzichte van de baseline werd berekend met behulp van de Cockcroft-Gault formule. Nierfunctiebepalingen werden gedaan indien dit nodig werd geacht en volgens de lokale richtlijnen voor het bepalen van de nierfunctie. Nierinsufficiëntie was gedefinieerd als een reductie in CrCl tot waarden tussen de 30 en 49,9 ml/min (matig-ernstige insufficiëntie) en minder dan 30 ml/min (ernstige insufficiëntie). De cumulatieve incidenties voor matig-ernstige en ernstige nierinsufficiëntie werden berekend. Relatieve risico's (RRs) en 95% BIs werden berekend voor factoren die mogelijk geassocieerd zijn met het optreden van nierinsufficiëntie.

Het merendeel van de patiënten was vrouw (n=213, 71,1%) en de gemiddelde leeftijd bedroeg 39,1 ± 11,1 jaren. De mediane CrCl bij start van de behandeling was 76,8 mL/min. Aan het eind van de studieperiode hadden 63 deelnemers (21,0%) nierinsufficiëntie ontwikkeld, 18,3% in de matig-ernstige vorm en 2,3% in de ernstige vorm. Tot de factoren die waren geassocieerd met het optreden van nierinsufficiëntie behoorden een toenemende leeftijd (RR=1,04 [95% BI, 1,03-1,06]) per jaar, lagere (per elke 1 ml) CrCL op baseline (RR=1,05 [95% BI, 1,04-1,08]), WHO hiv stadium III (RR=3,78 [95% BI, 1,42-10,06]) of stadium IV (RR=3,42 [95% BI, 1,16-10<09]) ten opzichte van stadium 1 en deelnemers met een Body Mass Index (BMI) <18,5kg/m^2 (ondergewicht, RR=3,87 [95% CI, 2,49-6,03]) vergeleken met patiënten met een BMI>18,5-24,9 kg/m2 (normaal gewicht). Patiënten met een of meer van deze risicofactoren zouden extra in de gaten gehouden moeten worden om nierinsufficiëntie te voorkomen.

Tenslotte is in hoofdstuk 3.3 gekeken naar de kennis en attitude ten aanzien van bijwerkingen bij patiënten die antiretrovirale middelen gebruiken. Alle patiënten van het KBTH die deze middelen gebruiken ontvangen voorlichting over therapietrouw en bijwerkingen. In een cross-sectioneel onderzoek is bij 98 patiënten een vragenlijst afgenomen. Deze vragenlijst bevatte vragen over sociaal-demografische gegevens, kennis over bijwerkingen van antiretrovirale geneesmiddelen en de houding van patiënten ten aanzien van deze bijwerkingen. De kennis werd vastgesteld op basis van een 3-punts

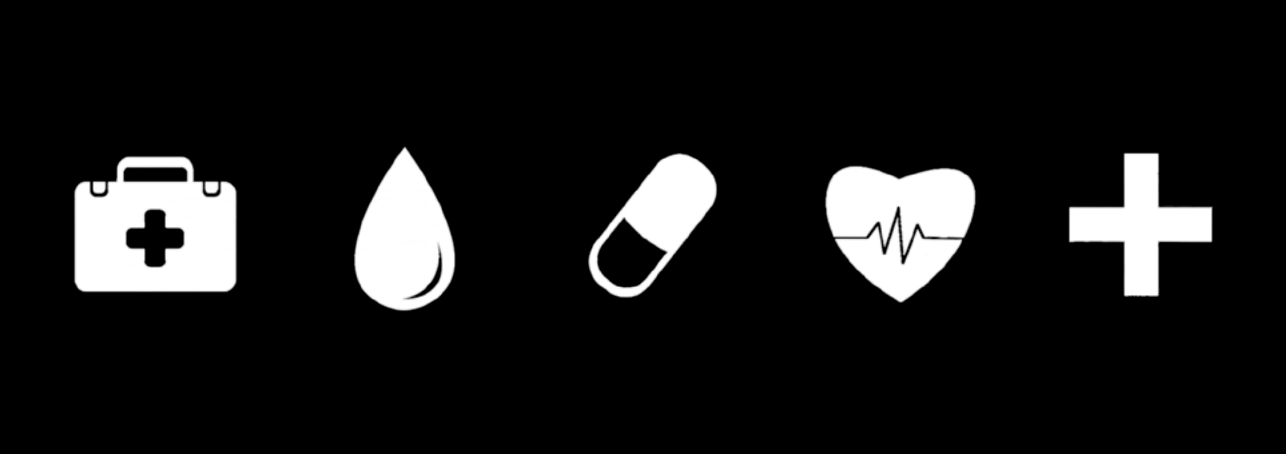
Likertschaal en de attitude op basis van een 5-punts Likertschaal. De gemiddelde scores werden bepaald en voor attitude werd een factoranalyse toegepast om relevante onderliggende constructen te identificeren. Van de geïncludeerde patiënten was 61% vrouw en het merendeel was 35-44 jaar (35%). Vrijwel alle patiënten (99%) gaven aan informatie te hebben ontvangen over bijwerkingen en 93% wist dat alle geneesmiddelen bijwerkingen kunnen hebben. Van alle patiënten onderschreef 90% de stelling dat geneesmiddelen zinvol zijn en je beter kunnen maken ten zeerste (gemiddelde score=4,87 ± 0,49), terwijl 27% de stelling dat geneesmiddelen bijwerkingen geven ten zeerste onderschreef (gemiddelde score=3,12 ± 1,55). Het merendeel van de deelnemers (74%) was het er ten zeerste mee oneens dat het niet nodig is bijwerkingen te melden bij een arts of apotheker (gemiddelde score=4,60 ± 0,83). De factoranalyse leverde twee onderliggende dimensies op (cognitieve en gedragsaspecten), die de houding van patiënten ten aanzien van bijwerkingen beschreven. Deelnemers aan dit onderzoek hadden een goede kennis van bijwerkingen en een positieve attitude ten aanzien van bijwerkingen. Voorlichting over therapietrouw en bijwerkingen aan patiënten die antiretrovirale middelen gaan gebruiken is zinvol en moet worden gecontinueerd.

Hoofdstuk 4 is de algemene discussie en het afsluitende hoofdstuk van dit proefschrift. De uit het onderzoek gebleken voordelen van het gebruik en de veiligheid van antiretrovirale geneesmiddelen worden hier gepresenteerd. Gezondheidswerkers met een grote kans op het via de huid in contact komen met door bloed overgedragen hiv kunnen baat hebben bij een goed en snelwerkend risicobeoordelingssysteem. Een dergelijk systeem blijkt een goede aanvulling te zijn in een setting waar de beschikbaarheid van testkits voor snelle diagnose van hiv beperkt is. Specifieke cohortstudies (cohort event monitoring) hebben bewezen van groot belang te zijn bij het genereren van informatie over de veiligheid van geneesmiddelen in landen met beperkte financiële mogelijkheden waar spontane rapportages van bijwerkingen te weinig gegeven genereren op een systematische manier. Het bewaken van bijwerkingen is in een land als Ghana belangrijk om te voorkomen dat patiënten onnodig switchen naar andere behandelingen. Het beheersen van bijwerkingen, bijvoorbeeld door dosisverlaging, en het kiezen van de juiste therapie helpt bij het verbeteren van therapietrouw bij mensen die antiretrovirale geneesmiddelen gebruiken en bij het vervolgens voorkomen van aanpassingen in de therapie. Tekortkomingen in laboratoriumvoorzieningen, gekwalificeerd personeel en een tekort aan reagentia leiden tot uitdagingen, bijvoorbeeld op het gebied van consistent monitoren van de (renale) effecten van het gebruik van tenofovir. Er zijn meer inspanningen nodig om het doen van klinische bepalingen bij mensen met hiv/aids prioriteit te kunnen geven. Tot slot lijkt het geven van voorlichting bij de start van antiretrovirale therapie nuttig, maar voortdurende bewaking van signalen van bijwerkingen en het stimuleren van patiënten om deze te rapporteren blijven nodig om de uitkomsten van antiretrovirale therapie te verbeteren.

In de afgelopen twee decennia hebben vele lage en middeninkomenslanden nationale geneesmiddelenbewakingscentra opgezet, maar weinig landen hebben een volledig

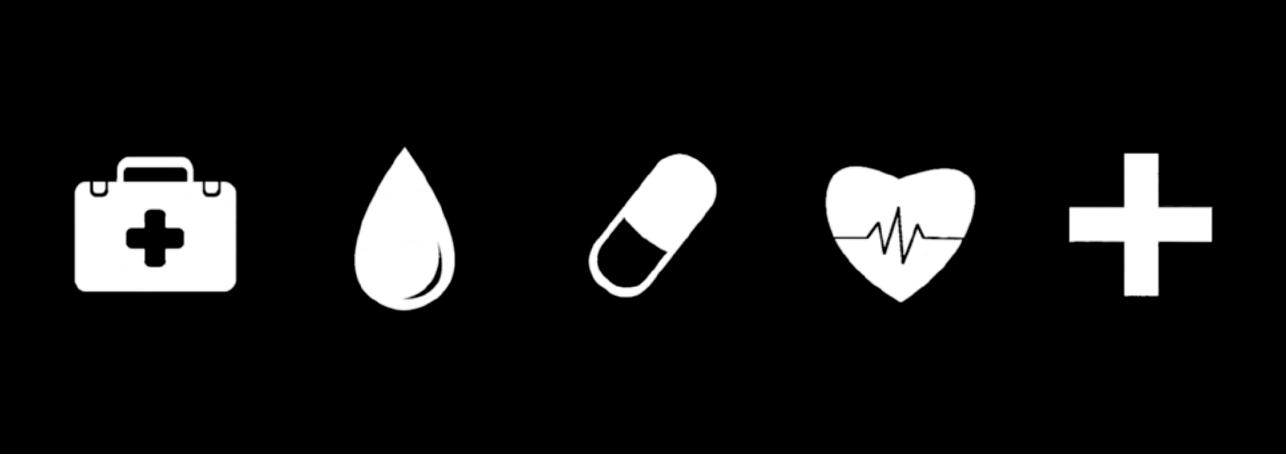
operationeel systeem. De bekwaamheid van medewerkers binnen deze instituten moet worden versterkt om de ontwikkeling, de oprichting, het functioneren en de duurzaamheid van een uitgebreid medicatieveiligheidssysteem te kunnen ondersteunen. De algemene bevolking moet tevens worden voorgelicht over de mogelijkheden van het spontaan melden van bijwerkingen en worden gestimuleerd hieraan bij te dragen. Apothekers en apotheken kunnen een leidende rol spelen bij de farmacovigilantie, ook door andere zorgverleners te wijzen op het bestaan van meldingsformulieren. Tot slot lijkt er een rol weggelegd voor sociale media.

Concluderend draagt dit proefschrift bij aan onze inzicht in het gebruik en de veiligheid van antiretrovirale middelen in Ghana, als pre- en postexpositieprofylaxe en als krachtige antiretrovirale therapie bij patiënten met hiv/aids. Voor de toekomst is samenwerking tussen belanghebbenden noodzakelijk om het benodigde bewustzijn te creëren dat farmacovigilantie aan de frontlinie van gezondheidsbeleid en de implementatie daarvan zou moeten staan. Alleen zo kan de veiligheid van patiënten die antiretrovirale geneesmiddelen gebruiken worden geborgd en gegevens worden gegenereerd die de wereldwijde kennis op dit gebied vergroten.



Chapter 6

ADDENDUM



Chapter 6.1

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ACKNOWLEDGEMENT

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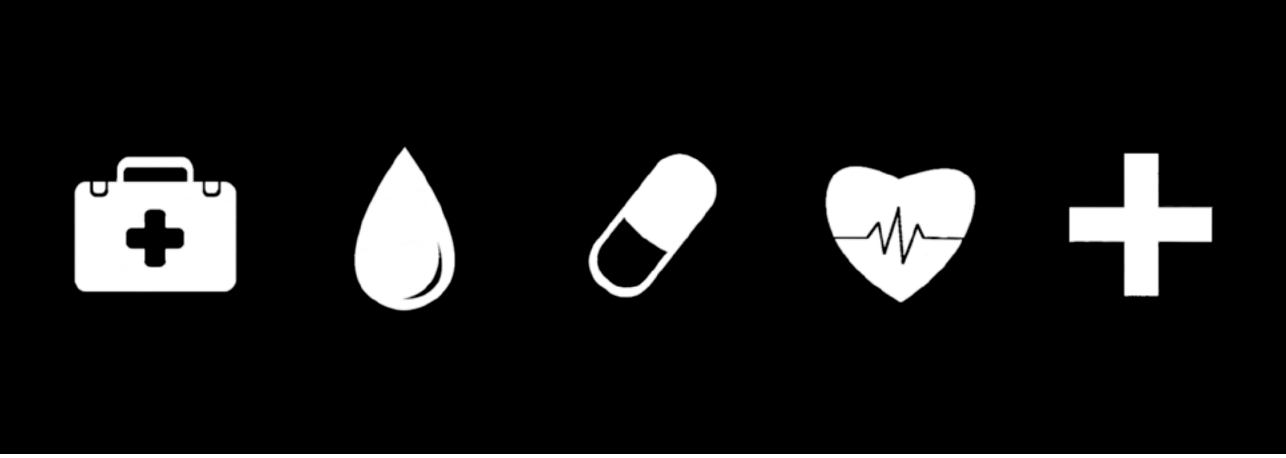
NYE YEWALA DON,
VA MULTUMESC,
THANK YOU.



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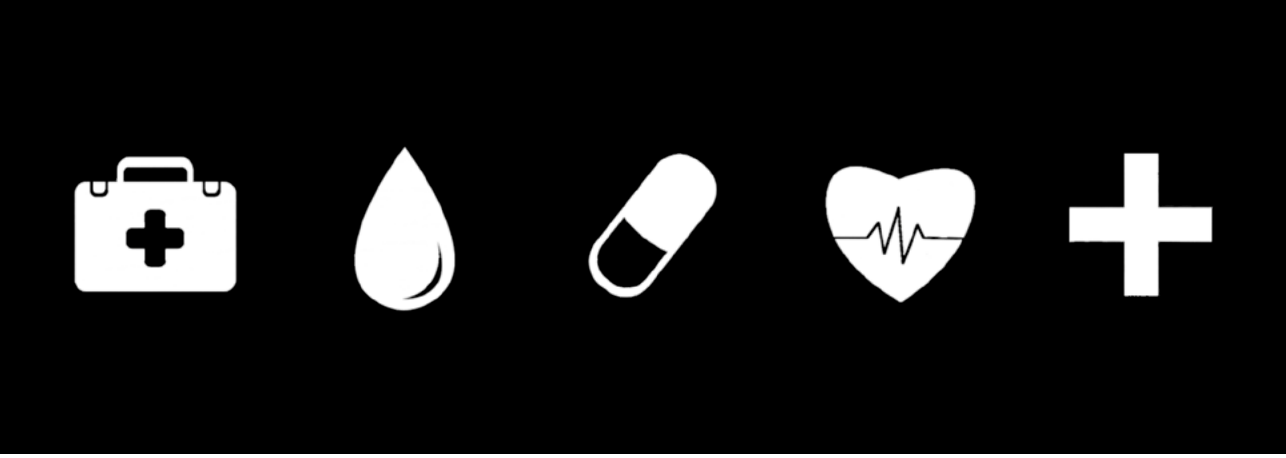

Chapter 6.3

LIST OF PUBLICATIONS

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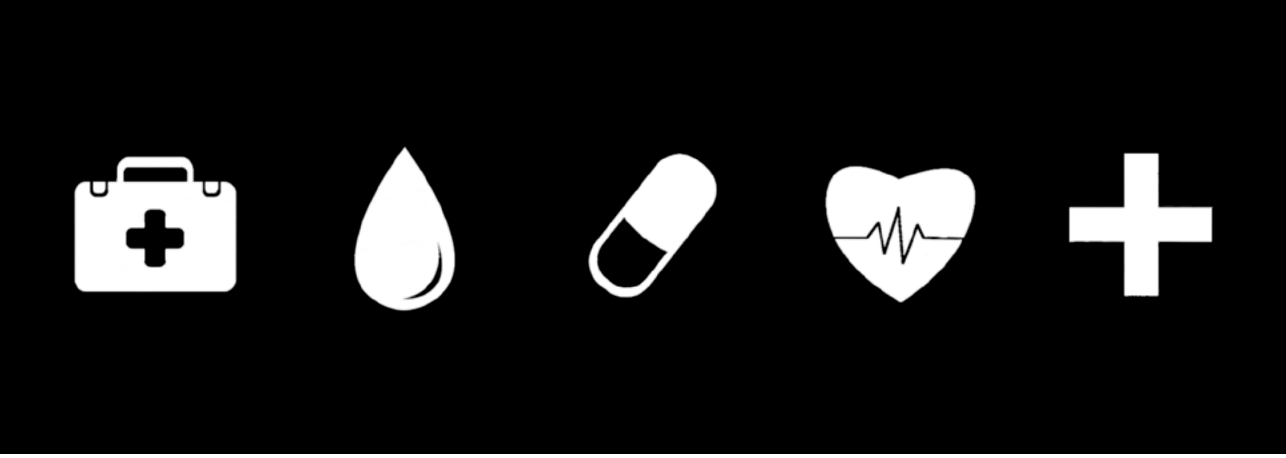

Chapter 6.4

ABOUT THE AUTHOR

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Raymond A. Tetteh is an accredited clinical pharmacy tutor practitioner with specialty in infectious diseases and internal medicine, who has worked in the Korle Bu Teaching Hospital of Ghana since 1988. He qualified as a pharmacist from the Carol Davila University of Medicine and Pharmacy in Bucharest, Romania in 1987. He later qualified as a clinical pharmacist with an MSc degree from the Robert Gordon University of Aberdeen, UK in 2001. After accreditation as a tutor practitioner by the Robert Gordon University, he started lecturing in various Schools of Pharmacy [University of Ghana School of Pharmacy (UGSOP), Kwame Nkrumah University of Science and Technology School of Pharmacy (KNUSTSOP) and the Central University School of Pharmacy (CUSOP)] on part-time basis. Presently, he holds the position of Consultant Clinical Pharmacist with special interest in HIV care stemming from an initiative of WHO to provide antiretroviral drugs for patients living with HIV/AIDS in resource-limited countries. Trained as a frontline health professional in all aspects of HIV clinical care, he was fully involved as a trainer of trainees in a scaling up program of providing ART to all corners of the country by the National HIV/AIDS/STI Control Program (NACP) of Ghana and is presently a member of the technical working group of the program. He supports the Department of Medicine in managing over 20,000 PLHIVs and other clinical conditions in internal medicine. He is an expert in Medicines Information Management, trained at the Medicines Information Centre (Groote Schuur Hospital) of the University of Cape Town, South Africa. He acted as deputy national coordinator in setting up a National Drug Information Resource Centre with peripheral centres in most hospitals in Ghana. He serves on the National Experts Committee on the Standard Treatment Guidelines and Essential Medicines List for Ghana. He also consults for the NHIA as an expert on the review of the National Health Insurance Medicines List and Price Review Committee. As a fellow of the Ghana College of Pharmacists and the West African Postgraduate College of Pharmacists, he lectures and examines in both Colleges. He has also served as a labour leader of hospital pharmacists since 1988.

In October 2010 he started the work presented in this thesis as a professional PhD student at the Utrecht-WHO Collaborating Centre for Pharmaceutical Policy and Regulation based at the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University in The Netherlands.