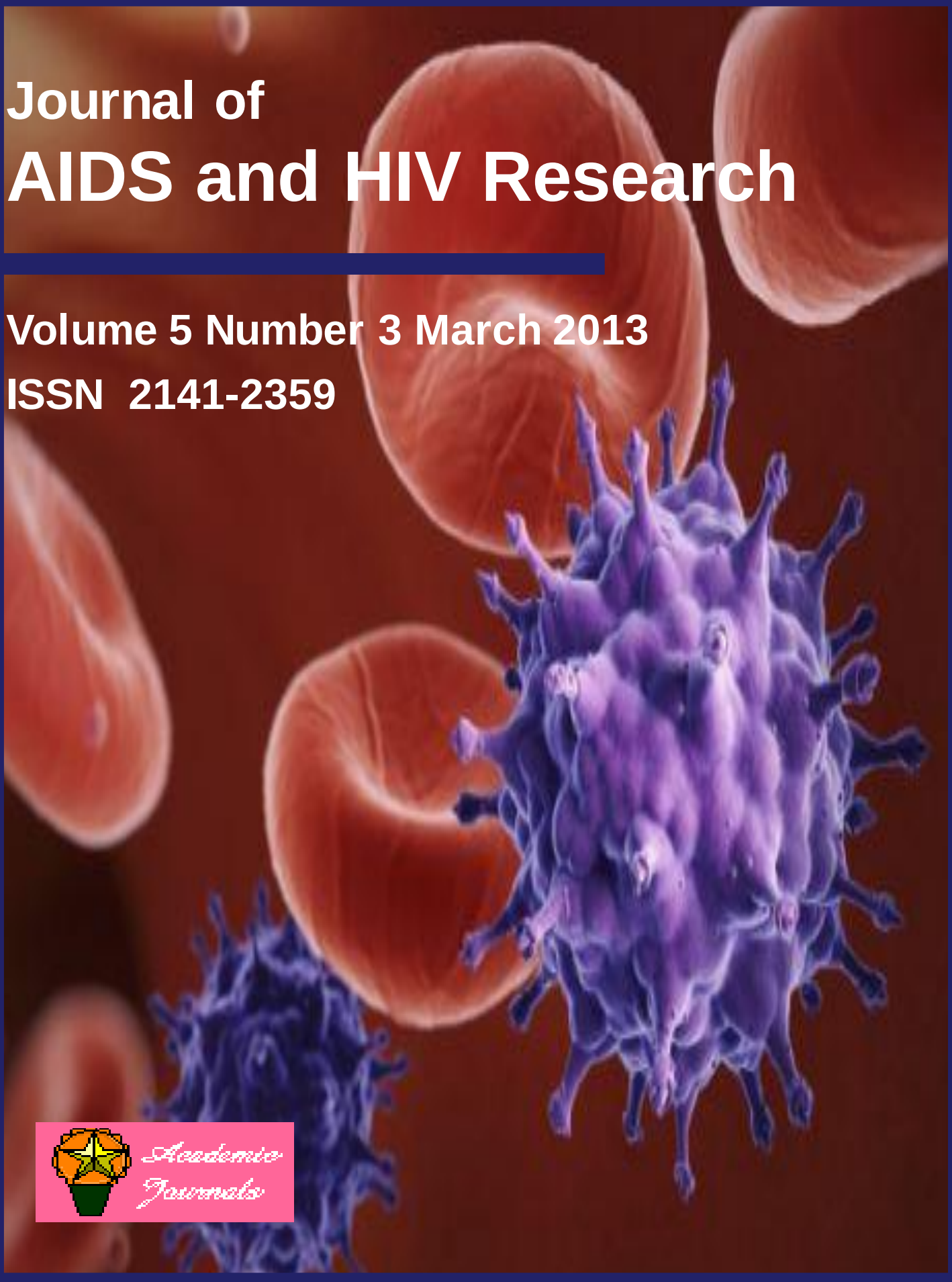

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Moran GJ, Amii RN, Abrahamian FM, Talan DA (2005). Methicillinresistant Staphylococcus aureus in community-acquired skin infections. Emerg. Infect. Dis. 11: 928-930.

Pitout JDD, Church DL, Gregson DB, Chow BL, McCracken M, Mulvey M, Laupland KB (2007). Molecular epidemiology of CTXM-producing Escherichia coli in the Calgary Health Region: emergence of CTX-M-15-producing isolates. Antimicrob. Agents Chemother. 51: 1281-1286.

Pelczar JR, Harley JP, Klein DA (1993). Microbiology: Concepts and Applications. McGraw-Hill Inc., New York, pp. 591-603.

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Journal of AIDS and HIV Research

Table of Contents: Volume 5 Number 3 March 2013

ARTICLES

Case Report

Research Articles

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Case Report

Elevated liver transaminases, human immune deficiency virus (HIV) seroconversion and rapid progression to AIDS in a HIV prevention clinical trial participant: A case report

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This is a case report on a human immune deficiency virus (HIV) prevention trial participant who HIV seroconverted, developed hepatitis and rapidly progressed to acquired immunodeficiency syndrome (AIDS). A 24 year old HIV negative, non-pregnant participant consented to participate in the FEM-PrEP clinical trial. Her baseline parameters were normal; she was on oral contraception and was vaccinated for hepatitis B. She attended monthly scheduled visits and protocol specific procedures were done. She HIV seroconverted at her week 36 follow up visit, and her aspartate aminotransferases (ASTs) and alanine aminotransferases (ALTs) were elevated to a grade 3 level (DAIDs grading). Over her next follow up visits, there were fluctuations in her AST and ALTs and she had a history of using herbal medication. She rapidly progressed to AIDS and was started on anti-retroviral (ARVs). The participant was in the Truvada arm of the study. This case of hepatic toxicity and rapid HIV progression demonstrates the clinical complexity of HIV management in clinical trials. We hypothesize that the hepatic toxicity was associated with acute HIV infection and concomitant use of herbal medicine; however, we cannot definitively demonstrate causality.

Key words: HIV prevention, seroconversion, elevated transaminases, STDs, liver toxicity, herbal medication, antibiotics, oral contraception, rapid progression to AIDS.

INTRODUCTION

FEM-PrEP clinical trial was a randomized, double-blinded, placebo controlled trial of daily oral tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, Truvada) as compared to a placebo conducted in Kenya, South Africa and Tanzania. The primary objective of this study was to assess the effectiveness and safety of daily oral Truvada when compared with placebo for HIV prevention among HIV-uninfected women who are at high risk of becoming HIV infected through sexual intercourse.

This is an interesting case report in an oral HIV Pre Exposure Prophylaxis (PrEP) prevention trial participant who HIV seroconverted and rapidly progressed to Acquired Immunodeficiency Syndrome (AIDS) with 4 months requiring anti-retroviral (ARV) therapy. She also developed a fluctuating hepatitis with liver transaminase levels rising up to grade 4 due to a number of possible causes including use of non- registered herbal medication.

Increased levels of liver transaminases are an indication of hepatocellular liver injury and can have

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Abbreviations: RFU, Regular follow up; **PRFU,** post regular follow up.

many causes, including but not limited to alcohol use, drug use, autoimmune diseases, infections and HIV acute infection (Limdi and Hyde, 2003).

The clinical features of acute retroviral syndrome are non-specific and often mimic other clinical entities. Common HIV seroconversion laboratory findings include leukopenia, thrombocytopenia, and elevated trans-aminases (Chen et al., 2010). This case report explores the participant's presentation of acute seroconversion, and possible causes for her increased liver transaminases.

CASE REPORT

A 24 year old participant consented to participate in the FEM-PrEP clinical trial in South Africa on August 9, 2009. Her baseline weight was 62 kg, she was not pregnant, was HIV, hepatitis B surface antigen (HBsAg) and surface antibody (HBsAb) negative, had adequate renal and hepatic function according to specified protocol criteria, normal phosphate levels and no proteinuria or glycosuria. She was on oral hormonal contraception (Triphasil™). She received the hepatitis B vaccination series as per protocol (first dose at enrolment visit and second dose at regular follow up (RFU) week 4 and the last dose at RFU week 24). Sexually transmitted infection (STI) testing for gonorrhoea, Chlamydia, trichomoniasis, syphilis and bacterial vaginosis at screening was negative. She attended monthly scheduled visits at the research centre which included HIV and risk reduction counselling, contraceptive counselling, and HIV and pregnancy testing. Hormonal contraception and male and female condoms were provided. In addition, sexual behaviour data were collected and study product was issued. Safety assessments included monitoring of renal (urine for glucose and protein, serum creatinine and phosphate) and hepatic functions: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at weeks 4, 12 and then quarterly.

Any abnormality was graded according to the DAIDS grading scale ("The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Bethesda, MD: National Institute of Allergy and Infectious Diseases, Division of AIDS, December 28, 2004.,"). Pregnancy testing was done at each follow up visit.

FINDINGS

At her RFU week 4 visit, her HIV test was negative and all safety tests were normal (Table 1). She had an abnormal vaginal discharge and was treated according to South Africa National Guidelines for syndromic management of STIs ("Standard Treatment Guidelines And Essential Drugs List For South Africa,"). RFU weeks 8, 12 and unscheduled visits were uneventful.

At her RFU weeks 20 and 24 visits, her HIV test was negative and safety tests were normal. She presented with recurrent acute tonsillitis which was treated with amoxicillin and paracetamol at both visits.

She presented at RFU week 28 with symptoms of a urinary tract infection (UTI) and abnormal vaginal discharge. Her urine showed leucocytes 3+ and vaginal swabs were taken for STI testing. HIV tests were negative and safety bloods were normal. She was treated for UTI and bacterial vaginosis (BV) based on laboratory results with ciprofloxacin and metronidazole. Hepatitis B surface antibody (HBsAb) tests showed immunity to hepatitis B, with antibody titers> 1000 mIU/ml. RFU week 32 visit was uneventful.

At her RFU week 36 visit (that is, SFU week 0 visit) on May 13, 2010, her HIV rapid tests were positive. Her AST and ALT were elevated to a grade 3 level (130 and 179 IU/L, respectively), serum creatinine and phosphate were normal. She reported having had another episode of tonsillitis. On advice of her local general practitioner, she stopped her study product 2 weeks prior to this visit. She was counselled appropriately regarding her HIV results. Study product was permanently withdrawn, because of her seroconversion. Her CD4 count was 338 cells/µl and polymerase chain reaction (PCR) viral load (VL) at week 36 visit was 660693 cp/ml (log 5.82). She had subtype C virus that showed no FTC or TDF resistance on genotyping (Table 1). An HIV PCR test was done retrospectively on a week 32 sample and was negative. She was referred to the local clinics for the clinical management of her HIV infection and joined the seroconvertor follow up sub-study of the clinical trial.

At a subsequent post seroconversion regular follow up visit (PRFU), two weeks later, her AST was 115 IU/L and ALT was 139 IU/L (grade 3). A week later she came for retesting and reported taking Chinese herbal capsules available over the counter as immune boosters.

At PRFU week 4, her transaminases improved to grade 2 toxicity (AST 62 IU/L and ALT 83 IU/L) and she presented with an abnormal vaginal discharge and an upper respiratory tract infection. She was treated with oral metronidazole and cotrimoxazole vaginal cream for BV and candidiasis based on laboratory results. The participant had not accessed the clinic for her HIV infection and indicated that she was not ready to do so.

Between PRFU week 4 and PRFU week 16 visits, her HIV VL increased to 1698243 cp/ml (log 6.2) and her CD4 count decreased to 127. Her transaminases fluctuated between grade 1 and 2 toxicity for the next 3 months (Table 1).

At her PRFU week 24, her transaminases increased to grade 4 (AST 402 IU/L and ALT 222 IU/L); tests for hepatitis A and C were negative. A week later, she reported the use of an herbal home-made medication; at this time her AST/ALT levels were grade 3. There was no self-reported history of alcohol use. She was advised to stop the herbal medication and AST/ALT tests were repeated over the next 2 months and fluctuated between grade 2 and 3. Her CD4 count at PRFU week 36 was 42 cells/µl. In January 2011, she was admitted twice to the local hospital for abdominal pain and was suspected to have peptic ulcer disease and pelvic inflammatory disease. The participant did not disclose her HIV status when admitted and was reluctant to access HIV care at the local HIV clinic despite continual counselling and

Table 1. ALT, AST Viral log, CD4 count, TDF and FTC levels per visit.

Date	Visit type	AST	ALT	VL log	CD4	TDF Di-PO4 f/mol	FTC Tri-PO4 f/mol	TDF (ng/ml)	FTC (ng/ml)
24/08/09	Screen	23	16	.	.	.	.	.	.
01/10/09	RFU 04	24	21	.	.	.	92500	31.93	51.05
29/10/09	RFU 08	.	.	.	.	.	56400	106.36	1818.06
26/11/09	RFU 12	20	19	.	.	.	.	.	.
22/12/09	US	.	.	.	.	.	25700	233.95	1590.82
21/01/10	RFU 20	.	.	.	.	386000	61100	20.98	36.15
19/02/10	RFU 24	18	28	.	.	10640000	1240000	113.17	1024.75
18/03/10	RFU 28	.	.	.	.	941000	.	.	.
15/04/10	RFU 32	.	.	.	.	68000	.	.	.
*13/05/10	RFU 36	130	179	5.8	338	.	.	.	.
02/06/10	PRFU 01	115	139	.	.	.	.	.	.
18/06/10	PRFU 04	62	83	5.8	366	.	.	.	.
15/07/10	PRFU 08	47	59	6	343	.	.	.	.
21/08/10	PRFU 12	56	59	6.2	309	.	.	.	.
14/09/10	PRFU 16	148	118	6.3	127	.	.	.	.
05/10/10	PRFU 20	missed		.	.	.	.	.	.
04/11/10	PRFU 24	402	222	.	.	.	.	.	.
05/11/10	US	598	332	6.4	188	.	.	.	.
11/11/10	US	228	179	.	.	.	.	.	.
18/11/10	US	211	149	.	.	.	.	.	.
30/11/10	PRFU 28	141	96	6.3	191	.	.	.	.
21/12/10	PRFU 32	358	254	.	.	.	.	.	.
18/01/11	PRFU 36	57	30	.	42	.	.	.	.
03/02/11	US	.	.	.	.	.	.	.	.
**05/02/11	.	.	.	.	.	.	.	.	.
24/02/11	PRFU 40	22	13	3.4	205	.	.	.	.
22/03/11	PRFU 44	.	.	.	.	.	.	.	.
21/04/11	PRFU 48	.	.	.	.	.	.	.	.
17/05/11	PRFU 52	.	.	2.0	377	.	.	.	.

RFU: Regular follow up visit by week; PFRU: post regular (seroconversion) follow up by week; US: unscheduled visit. *Seroconversion. **ARV commenced at clinic.

advice. At her PRFU week 36, she presented with oral candidiasis, generalised lymphadenopathy, night sweats and persistent abdominal pain. Abdominal tuberculosis was excluded by an abdominal sonar and chest X-ray. Her transaminases declined to grade 1 (AST 57 IU/L and ALT 30 IU/L).

On the 5th of February 2011, she started an ARV regimen: zidovudine (AZT), lamivudine (3TC) and efavirenz (EFV). On the 24th of February 2011 (PRFU week 40), her CD4 count had increased to 205 and VL decreased to 2754.23 cp/ml (log 3.44), and the transaminase levels had returned to normal.

On her last PRFU 52 visit, the participant had markedly improved after 4 months of ARVs and her CD4 count was 377, VL was 95.50 cp/ml (log 1.98). Her weight was 55.6 kg. She was committed to continuing her ARV therapy.

After the trial ended and unblinding occurred, it was confirmed that the participant was in the Truvada arm of the study and had detectable but varying plasma levels of tenofovir and emtricitabine at her RFU visits.

DISCUSSION

This is an interesting case report of a 24 year old woman, participating in an HIV prevention trial, who seroconverted and progressed rapidly to AIDS requiring ARV treatment. During her trial participation, her liver transaminases increased, which could have been due to a multiplicity of factors and/or combination of factors.

At her PRFU visit week 16, she had rapidly progressed to the clinical AIDS stage (CD4 <200) and needed ARV therapy. Her immune response to ARVs was dramatic, with a 3 log decrease in her VL and a significant increase

in her CD4 count within three weeks of starting medication. Phillips et al. (2001) concluded in their study that low CD4 counts and high VL at baseline were not associated with poorer virological outcomes, however, patients with greater than 100,000 c/ml had a slower rate of achieving viral suppression. We did not monitor her for complete viral suppression as she was exited from the study after week 52 visit as per protocol. She presented with tonsillitis and elevated transaminases at the sero-conversion visit. Both are features of acute HIV infection (Chen et al., 2010; Mata-Marin et al., 2009). An analysis of her biological and viral factors as contributing factors to her rapid progression as described by Khanlou et al. (1997) was not explored further as it was not part of the study protocol.

Rapid HIV progression

High plasma VL followed by low CD4+ counts, as well as rapid rate of decline in CD4, are significant predictors of progression in HIV/AIDS (Mellors et al., 1997). Mellors et al. (1997) reported an 80% risk of rapid progression to AIDS in patients in whom the VL is more than 30,000 cp/ml. In this participant, her baseline CD4 count was 338 cells/µl and her VL was 660693.35 cp/ml (log 5.82). Her CD4 count dropped to <200 cp/ml within 4 months. A uniform finding for rapid progressors is a high VL that does not fall dramatically after primary HIV infection (Khanlou et al., 1997), resulting in a high VL set point, as was evident in this participant as well.

Elevated liver transaminases

Elevated transaminases reflect damage to hepatocytes with leakage of AST and ALT in plasma, and can be a result of multiple factors including, drug use, alcohol use, viral infections, autoimmune diseases and herbal products (Giannini et al., 2005; Limdi and Hyde, 2003). In this participant, there are possibly multiple drugs including herbal medications contributing to her elevated transaminases.

Common therapeutic drugs as well as herbal remedies have been implicated as potential causes of hepatotoxicity (Giboney, 2005). Both tenofovir and emtricitabine can result in liver toxicity and elevated liver enzymes ("Investigator's Brochure: Emtricitabine/ Tenofovir disoproxil Fumarate tablets, 2nd edition 2005"), albeit rarely. The participant was in the Truvada arm and had detectable but varying plasma levels of tenofovir and emtricitabine prior to seroconversion. However, on the two visits before the seroconversion (week 28 & 32), her plasma levels were undetectable. At the visit before the seroconversion visit, she had a low intracellular TFV-DP level. This could be consistent with not having taken the drug within the last two weeks. Therefore, we may conclude that she was probably not taking the drug correctly during the time of becoming HIV infected. Her hepatic function tests whilst on Truvada prior to seroconversion were normal and the first elevation to a grade 3 was noted at the seroconversion visit.

In addition, antibiotics like amoxicillin, ciprofloxacin and metronidazole (rarely) can be associated with hepatotoxicity and liver failure (Fontana et al., 2005); "Metronidazole tablets BP 400 mg" (Wolfson and Hooper, 1989)'. Causality assessment of suspected drug-induced liver injury related to antibiotics can be difficult, particularly because some cases occur long after the drug has been stopped (Robles et al., 2010). Our participant was on three courses of amoxicillin prior to and at the time of seroconversion for the treatment of recurrent tonsillitis. In addition, she had a dose of ciprofloxacin and metronidazole prior to seroconversion. Causality to elevated transaminases due to amoxicillin, ciprofloxacin or metronidazole is unlikely as the participant's trans-aminases did decrease by her PRFU weeks 4, 8, and 12 visits and increased again without her being on antibiotics.

Triphasil is a low dose combined oral contraceptive (OC) containing 30 µg ethinyloestradiol and, 50 µg levonorgestrel. Dickerson et al. (1980) demonstrated that OCs with ethinyloestradiol content below 35 µg seem to have little effect on liver function. This participant was on triphasil from the onset of the study and we believed it is unlikely that the triphasil contributed to her increased transaminases.

Paracetamol in normal doses can, albeit rarely, cause hepatic toxicity as described by Kadas et al. (1998), but if it occurs, it is usually associated with additional factors such as alcohol intake and decreased nutrition. The participant reported no alcohol use and was well nourished, and thus we think that the paracetamol for her tonsillitis is not the cause of the elevated enzymes.

Traditional Chinese medicine is a complex mixture containing hundreds of different components (Wang et al., 2011). Some herbs have been documented as having both therapeutic and toxic effects on the liver, leading to the complex problem of distinguishing the benefits from the risks of using this herb (Wang et al., 2011). In this participant, her transaminases increased post seroconversion to grade 4 toxicity. She confirmed the use of herbal medication, both in the form of "Chinese herbal supplements" for immune boosting that she obtained over the counter at a local pharmacy, as well as home based preparations. As her transaminases fluctuated and her HIV progressed, she was advised to stop her herbal preparations. There may be an association between her elevated transaminases and the herbal medication evident by the elevation after PRFU week 12 visit, as well as the drop of the transaminases to a grade 1 after she reported stopping the use of these products. A study by Peltzer et al. (2008), in South African HIV positive men and women found that majority of recently diagnosed HIV

infected patients use herbal products for immune supplementation and symptomatic relief, with about 90% admitting to not revealing the use of the products to their health care providers.

Conclusion

Clinical HIV prevention trials, especially of PrEP, require meticulous follow up and monitoring of primary (HIV seroconversion) and secondary safety endpoints. This case of hepatic toxicity in a 24 year old lady demonstrates clinical complexity. She presented with acute seroconversion illness, had a rapid progression to HIV, severe elevation of liver transaminases and a delayed acceptance of her new HIV status. This led to a delayed start of ARV therapy in the presence of very low CD4 count and high VL. She responded dramatically to ARV therapy as evident by her rapid immune recovery and decrease in VL. We cannot be entirely certain regarding the aetiology of the hepatic toxicity. We hypothesize that the observed hepatic toxicity was associated with acute HIV infection and concomitant use of herbal medicine; however, we cannot definitively demonstrate causality or rule out other causes.

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Full Length Research Paper

Determinants of adherence to antiretroviral therapy (ART) among patients attending public and private health facilities in Nairobi, Kenya

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For maximum suppression of the multiplication of the human immunodeficiency virus (HIV) virus and subsequent increase in the CD4 cell count, a level of adherence of 95% and above is required among the patients on Antiretroviral drugs (ARVs). Most patients on antiretroviral therapy (ART) in Nairobi are not achieving the optimum adherence level required to maintain treatment efficacy, hence the risk of drug resistance and increased burden in the public health care system. The aim of this study was to identify the factors that influence adherence to ART among HIV patients attending public and private health facilities in Nairobi, Kenya. A non-interventional cross sectional study using both qualitative and quantitative data collection methods was used. The study was carried out in the Public and Private Health facilities offering ART in Nairobi, Kenya. Four hundred and fifty People living with HIV and acquired immune deficiency syndrome (AIDS) (PLWHA) receiving ARVs in selected public and private health facilities in Nairobi, between June, 2007 to June, 2008 were selected for the study. The composite adherence ART level among patients in Nairobi was found to be 85%. The major factors that were found to constrain adherence were costs, lack of social support, side effects, time to reach the health facility, and adequate knowledge of ARVs. This study found out that majority of the patients on ART in Nairobi are not achieving optimum adherence. The major factors that lead to the sub-optimal adherence are lack of social support, lack of disclosure that one is taking ARVs, poor knowledge of ARVs, associated costs such as transport and extra food requirements and the existence of side effects.

Key words: Optimal adherence, high risk sexual behavior, adherence to ART, knowledge about HIV and ART, side-effects, disclosure, treatment costs, discrimination, access to art, service providers.

INTRODUCTION

We are in the third decade of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) which has become the most important infectious epidemic disease in the last century. The 2008 United Nations Programme on HIV/AIDS (UNAIDS) epidemic update estimated that more than 33 million people worldwide are currently living with HIV/AIDS, with 2.7 million new infections and 2.0 million deaths due HIV in the year 2007 alone. Sub-Saharan Africa is the most severely affected region with over 22 million people living with HIV/AIDS as at the end of 2007 (UNAIDS/WHO, 2008). Kenya is one of the countries majorly hit by the worldwide HIV epidemic, having a population of more than 1.4 million people infected with HIV (UNAIDS/WHO, 2008; National AIDS and STI Control Programme, Ministry of Health, Kenya, 2008).

Anti-retroviral therapy (ART) has been successful in dramatically decreasing the morbidity and mortality caused by HIV. These successes coupled with the availability of lower-priced drugs, availability of generic drugs and an increase in donor funding has led many developing countries such as Kenya to implement and scale

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up HIV treatment programs for its HIV positive citizens (Pallela et al., 1998). A major concern in scaling up the ART is the emergence of drug-resistant viral strains as a result of sub-optimal adherence. To prevent the emergence of such strains, optimal patient adherence to ART is necessary. Levels of adherence in excess of 95% are required to ensure treatment success, adequate viral load suppression, improved immune status and slowing of the disease progression (Paterson et al., 2000).

To date, there is very little scientific data on the level of treatment adherence and the factors that may constrain adherence in Nairobi. This study was designed to determine the factors influencing adherence to ART among patients undergoing treatment in selected public and private health facilities in Nairobi Province, Kenya.

MATERIALS AND METHODS

This was a non interventional descriptive cross-sectional study comprising the patients receiving ART in selected public and private health facilities in Nairobi. Various data collection techniques were employed in this study. The selection of the number of study subjects was proportionate to size, based on the number of registered clients at the facility, whereby a proportion of the registered patients in selected facilities were asked to participate in the study. Systematic sampling was used to identify the patients to be interviewed at the clinics. Primary data was collected from the PLWHA on ART through semi-structured questionnaires in which a total of 450 patients were interviewed. Additional qualitative data was obtained through 8 Focused group discussions (FGDs). The participants were asked about what they knew about ARVs and whether they thought ARVs were a cure for HIV or not. The knowledge about HIV and ARVs was rated using eight questions worth one point each.

A total of 48% of the participants got a score of at least 75%. For the purpose of evaluating the impact of knowledge on adherence, a cutoff of 75% was used (> 75% good knowledge). The respondents were asked eight questions testing their knowledge on HIV and AIDS, as well as ARVs. Those who got six questions correct were awarded the 75% mark. Data checking and cleaning were done simultaneously during data collection. At the end of every field day, data was checked for completeness and consistency, and FGDs transcribed. After transcribing and cleaning, quantitative data was analyzed using the Statistical package for social sciences (SPSS). Hypothesis testing was done using Chi-square test. Independent predictors of lower adherence were determined using logistical regression analysis. A p value of < 0.05 was considered significant.

Setting

The data was collected from both private and public health facilities. The public health facilities have a comprehensive care center where the patients are provided with free HIV care while in the private facility, the patients pay for the services. In Kenya, the policy is to initiate treatment in patients with documented HIV infection and have met World Health Organization (WHO) stage IV disease, irrespective of CD4 cell count, or advanced WHO stage III disease, including persistent or recurrent oral thrush and invasive bacterial infections, irrespective of CD4 cell count or total lymphocyte count. Another consideration was also for the patients with a CD4 cell count of 200 per mm^3 or less for patients in WHO stage I, II or III of having tuberculosis with a CD4 cell count of 200 to 350 mm^3.

RESULTS

A total of the four hundred and fifty patients attending both private and public health facilities in Nairobi were involved in the study, with 60% of them being females. Slightly more than half of the respondents (53%) were married, and the highest age group was 30 to 35 years. Table 1 shows a summary of the selected socio-demographic characteristics of the respondents.

The study participants were asked to state the reasons for deciding to take an HIV test. The results indicated that a relatively high percentage of the respondents (53%) got to know their status while undergoing treatment. Other reasons included a desire to be tested after learning their partner had tested positive (15%), expectant and undergoing prevention of-mother-to-child transmission (PMTCT) (14%) and 3% as a condition for overseas travel, and this forced them to test. Finally, only 12% specifically went to check for their HIV status. Figure 1 summarizes the reasons for taking an HIV test among the respondents. The results indicated that of the patients who were taking the drugs, nearly half (48%) accurately knew what ARVs were, with slightly over half (52%) not knowing what it was.

With regard to experiencing of any side effects of using ARVs, the results indicated that a large proportion of the respondents (87%) had experienced some side effects, with only 13% stating they had not experienced any side effects. The results indicated that there was a significant relationship between the experiencing side effects of ARVs and adherence. It showed that majority of the respondents who had experienced some side effects were less likely to adhere to the treatment since they took some time dealing with the side effects. These results agrees with those found by Burgos et al. (1998) who also found out that the existence of side effects is likely to influence adherence levels. The results indicated that nearly half 196 (49%) of the respondents had missed some medications, with just over half of the respondents having not missed any of the medication. There were a variety of reasons that made the patients to miss medication, namely experience of side effects, lack of social support, hiding medicines, associated costs of transport and food, among others. This results agrees with earlier results which postulated that the likelihood of a patient's adherence to a given regimen declines with polypharmacy, the frequency of dosing, the frequency and severity of side -effects, and the complexity of the regimen (Green, 2003).

The patients were asked if they had disclosed to anyone that they were taking ARVs. The results indicated that for the many of the respondents, 35% disclosed to their spouses that they were taking ARVs. Others to whom they disclosed the information on taking ARVs included the siblings (25%), parents (14%) and friends (9%). It is also worth noting that 17% of the PLWHA had never informed anyone they were taking ARVs. Figure 2 shows the results of disclosure that one is taking ARVs

Table 1. Distribution of the subjects according to selected socio-demographic characteristics (n = 450).

Characteristic	No. of subjects	%
Age (years)		
18-24	50	11
25-29	76	18
30-34	127	29
35-49	95	22
Over 40 years	89	20
Sex		
Male	170	38
Female	280	62
Marital status		
Single	171	38
Married	239	53
Separated/divorced	40	9
Highest level of education		
No formal education	13	3
Primary	87	19
Secondary	122	27
Tertiary	228	51
Employment status		
Employed	224	49
Not employed	226	51

Further, the respondents were asked if they have ever had to change treatment since they started medication. The results indicated that about 45% had at least changed treatment regimen. On probing to establish the reasons that compelled them to change the treatment regimen, the results indicated that majority (58%) had changed the medication because of side effects, another 25% was due to unavailability of drugs while 17% changed the treatment due to treatment failure.

The participants were asked to estimate in time how much time they took by public means to travel from home to the heath facility, the results indicated that majority (35%) took between 30 min to 1 h to get to the facility, others took less than 30 min (28%), 1 to 2 h (16%) and more than 2 h (19%). This showed that a significant number of patients took a long period of time to get to the facility (χ^2 = 40.276, df = 3, p = 0.00). The duration taken to the health facility was found affect the level of adherence. Table 2 shows the results of the relationship between duration taken to travel to hospital and adherence level. The results when cross tabulated indicated that the duration taken to the health facility influenced the level of adherence, with 92% of those who achieved optimum adherence level having to travel only 1 h or less to the health facility.

Table 2. Relationship between duration taken to travel to hospital and adherence level.

Duration	Below optimum (%)	Optimum (%)	Total (%)
< 30 min	0 (0)	80 (33)	80 (26)
30 min-1 h	28 (44)	108 (44)	136 (44)
1-2 h	11 (17)	39 (16)	50 (16)
> 2 h	14 (22)	26 (11)	40 (14)
Total	63 (21)	243 (79)	306 (100)

With regards to the cost of travel to the health facility, results indicated that there was a wide discrepancy in the amount of money spent, based on the mode of transport used. The lowest amount spent was USD 0.25 and the highest amount of money spent was USD 6.25. The mean amount of money spent on transport was USD 2.13. The median was USD 1.75, mode USD 1.25 and the standard deviation was USD 1.375. Figure 3 shows the distribution of respondents by traveling expenses

DISCUSSION

The results indicated that just about half [216 (48%)] of the PLWHA had accurate knowledge of what ARVs were and what they do to the body. There was a significant relationship between knowledge of ARVs and adherence, with those having more accurate knowledge more likely to adhere (χ^2 = 106.432 df = 7, p = 0.001). There was a correlation between the knowledge level and the level of adherence with those with higher knowledge tending to adhere to treatment more than those with lower level of knowledge. The results of this study concurred with the study by Wenger et al. (1999) which stated that a good level of understanding about HIV by the patient, a belief that ART is effective and prolongs life, and recognition that poor adherence may result in viral resistance and treatment failure, all impact favorably upon a patient's ability to adhere. Conversely, a lack of interest in becoming knowledgeable about HIV and a belief that ART may in fact cause harm, adversely affect adherence (Wenger et al., 1999).

The results showed that majority of the respondents (87%) had experienced some side effects, with only 13% stating they had not experienced any side effects. These results concur with those found by Paterson et al. (2000), who also found out that the existence of side effects is likely to influence adherence levels (Burgos et al., 1998). The results also indicated that for the majority of the respondents, their spouses (35%) were aware that they were taking ARVs. The results indicated that those who had disclosed to the relatives and friends that they were taking ARVs were more likely to adhere to treatment because they had support from them. However, those who had kept the fact that they were taking ARVs secret were

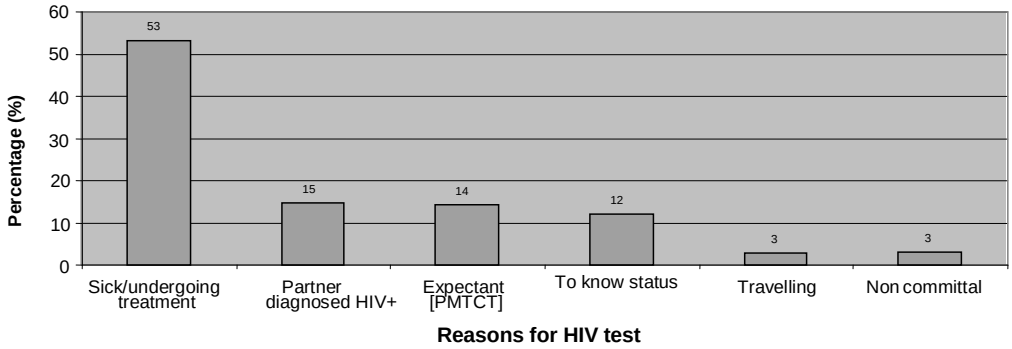

Figure 1. Distribution of respondents based on reasons for HIV test.

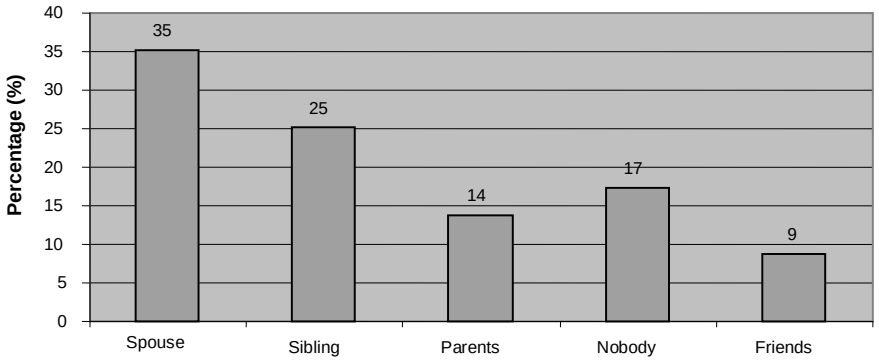

Figure 2. Distribution of Respondents based on whom they disclosed to that they are on ARVs.

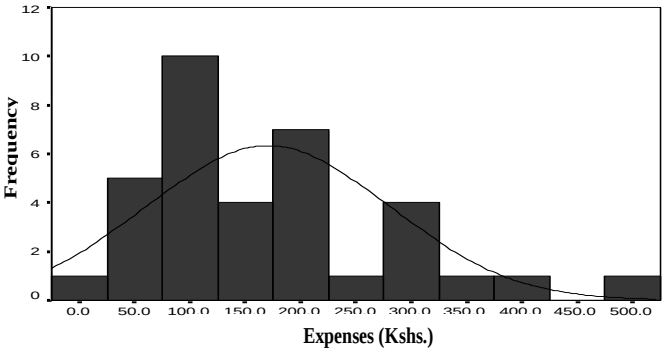

Figure 3. The distribution of respondents by traveling expenses.

more likely to default because the time for taking the drugs would come when they were with other people and this would make them default, as they had to hide. The results also concur with that by Green (2003), who said that living alone and a lack of support had been associated with an increase in sub-optimal adherence, and social isolation was predictive of sub-optimal adherence. Not living alone, having a partner, social or family support, peer interaction, and better physical interactions and relationships are characteristics of patients who achieve optimal adherence (Motashari and Riley, 1998).

CONCLUSIONS AND RECOMMENDATIONS

This study found out that majority of the patients on ART in Nairobi were not achieving optimum adherence. The major factors that led to the sub-optimal adherence were lack of social support, lack of disclosure that one was taking ARVs, poor knowledge of ARVs, associated costs such as transport and extra food requirements, and the existence of side effects. The health facilities offering ART should employ adequate numbers of well trained staff, as this will help cope with increasing workloads in the ART clinics, and it will also help reduce the long waiting times. There is also need to train staff in adherence counseling and continuously update their knowledge of HIV and AIDS, as this will help all the staff in the ART facilities to be able to participate in adherence counseling rather than leave it to the pharmacists only. Also, there should be sustained community mobilization

aimed at mitigating stigma and discrimination, in an effort to create an environment in which people can disclose and take their ARVs without fear of discovery.

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Full Length Research Paper

Human immunodeficiency virus (HIV) positive females in Saudi Arabia: Pregnancy and neonatal outcome

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This study was aimed to describe the demographic, presentation, clinical manifestation, and outcome of human immunodeficiency virus (HIV) positive females in Saudi Arabia. Special attention was drawn to the outcome of HIV positive pregnant females. A retrospective cohort study was conducted to evaluate HIV positive patients who presented to the emergency room and out-patient department in King Abdulaziz University Hospital (KAUH) between 1st of January, 2001 and 30th of December, 2010. Data wre collected from the medical records of the medical ward, outpatient clinic and discharge summary registry. The data included: age, chief complaint, investigation results upon admission, progress of the disease and whether the partner was informed and/or screened. A total number of 195 HIV patients were included in the study. The majority presented with fever and respiratory symptoms. Out of the 195 patients, 10 were pregnant, of which 3 patients died soon after admission, 6 presented with serious complications and only 1 patient was diagnosed early and received optimum treatment resulting in an HIV negative baby. Fetal outcome consisted of 7 living newborns; of these, 6 were HIV-positive (85.7%), of which 2 were breastfed (33.3%). The true prevalence of HIV remains unknown especially in the Middle East. Limited testing for patients at high risk of HIV often results in many missed cases particularly in pregnancy, where early detection and treatment could give the baby a chance of an HIV free life, which is the ultimate goal.

Key words: Human immunodeficiency virus (HIV), pregnancy, fetal outcome.

INTRODUCTION

In a conservative society, where discussing sexually transmitted diseases is considered a taboo, the increasing prevalence of these diseases has become evident (Tariq, 2006). The real question is whether denying the increasing prevalence of the problem will serve to improve or further worsen the situation? Are we really immune?

Sexually transmitted infections are one of the most under diagnosed health problems worldwide. They are rapidly becoming a progressive threat to society. Despite their being common, their variable presentations and asymptomatic status of unaware and sexually active individuals makes it difficult to track them. HIV was included in the notifiable diseases in Saudi Arabia back in 1984 (Tariq, 2006). However, the lack of awareness of the general public, health workers, and officials has contributed to limitations in its diagnosis, screening and estimating the prevalence of the disease (Fageeh, 2009).

Previous studies have shown that early detection of asymptomatic Human immunodeficiency virus (HIV)-1 infection may help in controlling the spread of infection and at the same time might better the prognosis (Kitahata et al., 2009). The presence of symptoms correlates with a more rapid progression to Acquired immunodeficiency syndrome (AIDS) (Buchbinder et al., 2005). The risk of progression to an AIDS-defining diagnosis within three years following seroconversion was substantially higher in those with acute symptoms lasting more than 14 days than in those who were asymptomatic or had only mild symptoms (78 and 10%, respectively) (Pedersen et al.,

1989). This necessitates the screening of HIV by health-care providers before patients become symptomatic, to allow for a better prognosis.

Our aim is to highlight the importance of early detection and a management approach to HIV patients in Saudi Arabia.

MATERIALS AND METHODS

The study was conducted in King Abdulaziz University Hospital (KAUH), which has a full operational capacity of 895 beds. It provides a spectrum of tertiary health care services to the community. It is a retrospective cohort study done to evaluate HIV positive patients who presented to the emergency room and out-patient department in KAUH between 1st of January, 2001 and the 30th of December, 2010. Patients enrolled in the study presented with an AIDS-defining illness. The detection of the disease depended on HIV testing and was confirmed by CD4 cell count and HIV ribonucleic acid (RNA) level at detection.

HIV cases are detected and screened mainly based on clinical suspicion. Enzyme linked immunosorbent essays (ELISA) are used for both HIV-1 and HIV-2 testing. Positive ELISA is confirmed by a Western blot test. The expanded World Health Organization (WHO) was used to define AIDS (Tariq, 2006). The Ministry of Health (MOH) is notified of all the positive cases. They are then referred to a tertiary governmental HIV centre and are treated with Highly active antiretroviral therapy (HAART). The cases are then followed up by testing for HIV viral load and CD4/CD8 counts.

Data was collected from the medical ward, outpatient clinic, and discharge summary registry for HIV positive patients. This included: age, chief complaint, investigation results upon admission, progress of the disease and whether the partner was informed or screened. Annual reports that are issued and used by the concerned officials in the MOH are not made available for the public. Approval from the ethical committee was obtained.

RESULTS

The total number of HIV positive patients was 195. The mean age of the patients was 41.14 years. The eldest patient was 73 years old and the youngest was a new-born. The female to male ratio was almost 1:1, with 107 female patients to 94 male patients. Out of 195 patients, only 31 (15.8%) were Saudi patients (Table 1). A total of 136 patients (69.74%) presented through the emergency room while 59 patients (30.02%) presented through the Outpatient department. The main presenting symptoms were fever, in 94 patients (48.20 %), cough in 66 patients (33.84%), chest pain in 41 patients (21.02%), vomiting in 37 patients (18.9%) and nausea in 32 patients (16.41%). However, a significantly smaller number of patients complained of diarrhea [9 patients (4.6%)] (Table 2).

With regards to marital status, 99 patients (50.77%) were married while 49 patients (25.13%) were single (Table 3). 10 of these patients were pregnant. Their mean age was 29 years, the eldest being 41 years old and the youngest being 17 years old. One patient was of Saudi nationality and the rest were from neighboring countries. All of them were married except for one who presented with septic abortion. Five of them (50%) presented in their first pregnancy, 2 (20%) were Para 2, with no living children, 1 had 3 pregnancies with only 2 living children, and 2 had two living children. The infection was not diagnosed during the present or the previous pregnancies in 70% of the cases and in none before 20 weeks of pregnancy. The screening of the sexual part-ners was not documented in any medical record since it is not obligatory. Two patients presented in labor, while the others presented with serious complications (septic shock, pulmonary tuberculosis (TB), abdominal TB, convulsions, breast abscess).

Out of 7 living newborns, 6 babies were infected, 2 of which were breastfed. During the study period, among the cases properly monitored, only one newborn (10%) was not infected with HIV (Table 4).

DISCUSSION

The incidence of HIV has reached unprecedented figures recently. As of December, 2009 more than 35 million had died since the onset of the epidemic, 33 million were estimated to be living with HIV/AIDS, where more than 50% of them are women (UNAIDS, 2010). Morbidity and mortality rates during pregnancy have doubled, affecting both mother and fetus simultaneously. 25 million children have been orphaned and 2.5 million children are living with HIV/AIDS (UNAIDS, 2008).

Each day, 7,000 people are newly infected with HIV, with increasing numbers among young adults, women, and children (Pedersen et al., 1989). These numbers are only likely to rise unless more aggressive prevention campaigns and intervention programs intercede to slow the pace of the epidemic (UNAIDS, 2009).

In Islamic countries, limited information is available regarding the true prevalence of HIV/AIDS (Abu-Raddad et al., 2010; Obermeyer, 2006). Since risky sexual behavior is forbidden in Islam. HIV/AIDS is assumed to be of very low prevalence. A local study performed in Riyadh included 74,662 individuals who presented for the obligatory premarital screening program for HIV/AIDS showed that the prevalence is 0.03%. This may suggest that we fall among the lowest prevalence worldwide. This study however fails to reflect definite figures as it was executed on a limited number of individuals who knew they were being screened and did not include a diverse age group (Abu-Raddad et al., 2010). Other local studies showed that the incidence of HIV in Saudi Arabia is escalating (Tariq et al., 2004; Al-Mazrou et al., 2005).

In Saudi Arabia, HIV testing is not included in the routine antenatal screening program. This might be attributed to the belief that the population fall within a low

Table 1. Distribution of HIV positive patients among different nationalities.

Nationality	HIV positive patients
Somalian	42
Chadian	46
Nigerian	2
Yemeni	30
Sudanese	11
Saudi	31
Eritrian	4
Indonesian	7
Bangladesh	3
Ethiopian	4
Egyptian	4
Palestinian	5
Unknown	6

Table 2. The marital status of the HIV positive patients.

Marital status	HIV positive patients
Married	99
Divorced	12
Widowed	15
Single	49
Unstated	20

Table 3. Depicts the presenting symptoms of the HIV positive patients.

Symptom	HIV positive patients
Fever	94
Headache	12
Myalgia	0
Arthalgia	22
Loss of appetite	1
Nausea	32
Vomiting	37
Lymphadenitis	7
Cough	66
Sore Throat	2
Diarrhea	9
Chest Pain	41
Fatigue	1
Shortness of breath	3
Weakness	7
Confusion	5
Body aches	28
Weight Loss	14

risk group. Hence, no voluntary counseling and testing (VCT) program was developed to help provide life-sustaining care for those living with HIV (Kabbash et al., 2010). Even though patients with HIV receive the maximum possible health care, counseling can serve as a preventive tool by advising HIV negative patients on how to reduce exposure and stay negative.

In this study, majority of the patients (136 patients [69.74%]) presented through the emergency room. Out of 195 patients, 27 patients (13.45%) died soon after admission to the hospital. This shows that patients presenting to the hospital were already in an advanced stage of their illness. Out of 10 pregnant patients, 3 (30%) died within a few days of admission. The high mortality rate is mainly due to their presentation at a terminal stage. The poor fetal outcome is also related to the late presentation, where out of 10 pregnancies, only one baby (which received an early diagnosis and management) was HIV negative.

Out of 10 pregnancies, 5 babies were discharged with the mother, 3 were breastfed by the mother due to late diagnosis. This has increased their chance of becoming infected due to a 30 to 50% transmission rate (Birkhead et al., 2010). If patients were diagnosed early, an elective caesarian could have been opted for, patients would have been warned against breastfeeding, reducing the risk of perinatal transmission to less than 2% (Birkhead et al., 2010). Mother to child transmission has been virtually eliminated in a relatively short period of time (Ellis et al., 2002). This was achieved in countries where intense, comprehensive public health program has maximized the benefits of advances in both diagnosis and treatment of HIV infection (Fowler and Newell, 2002; Brocklehurst and French, 1998). A similar experience was reported in a local study conducted in Riyadh (Edathodu et al., 2010). The health care providers of these cases were not able to take the necessary precautions, which is attributable to the absence of results. Although the risk of exposure is limited, nevertheless the enormity of the disease makes even the smallest mistakes unforgivable to any victim.

HIV transmission to a healthcare provider could be from the patient's various secretions on the mucosa (amniotic fluid, blood, urine, etc) where the incidence is 0.09% (Mofenson and Committee on Pediatric AIDS, 2000; Henderson et al., 1990). Another mode of transmission could be by a needlestick injury where the incidence is 0.36%, according to a report from the Centers for Disease Control (CDC) Cooperative Needlestick Surveillance Group (1993) (Henderson et al., 1990). Another meta-analysis reports the risk to be 0.23%. That risk can be eliminated by more than 80% by simple precautions such as cleaning the affected area with the affected area with alcohol and giving the affected person

Table 4. Clinical profile of HIV-positive pregnant women at KAUH, 2001 to 2010.

Presentation status	Age (years)	Parity	Nationality	Mode of delivery	GA (weeks)	Result of HIV screen at time of presentation	Fetal outcome	Breastfed	Maternal outcome
Eclampsia, convulsion, unconsciousness, genital warts	41	P2 (no living children)	Nigerian	CD	30	Not available	Stillborn	No	Died 2 days post admission
Septic shock, generalized lymphadenopathy	30	P0	Sudanese	SVD	32	Not available	IUFD	No	Died 2 days post admission
Abdominal TB	28	P3 (2 living children)	Saudi	SVD	39	Available. Diagnosis made at 4 weeks of pregnancy	2.4 kg/HIV negative	No	Referred to an infectious center
In labor	25	P2 (no living children)	Somali	SVD at home	40	Not available. Diagnosis made 4 months post-SVD	3.3 kg/ HIV positive	No	Died 1 year post admission
Breast abscess	27	P2 (2 living children)	Chadian	SVD	40	Not available	3.0 kg/ HIV positive	Yes	Referred to an infectious center
Severe GIT symptoms	33	P2 (2 living children)	Somali	SVD	38	Available. Diagnosis made at 22 weeks of pregnancy	2.5 kg/ HIV positive	No	Referred to an infectious center
In labor	21	P0	Somali	SVD	29	Not available	1.2 kg/preterm/ HIV positive	No	Referred to an infectious center
Pulmonary TB, genital warts	40	P0	Nigerian	SVD	34	Available. Diagnosis made at 20 weeks of pregnancy	1.7 kg/ HIV positive	No records	Referred to an infectious center
In labor	17	P0	Yemeni	SVD	40	Not available	3.0 kg/ HIV positive	Yes	Referred to an infectious center
Septic shock, GIT symptoms, genital ulcer	28	P0	Chadian	Induced abortion	8	Available. Diagnosis made within 14 hours of presentation	Abortion	No	Referred to an infectious center

CD, cesarean delivery; GA, gestational age; GIT, gastrointestinal tract; IUFD, in utero fetal demise; KAUH, King Abdulaziz University Hospital; SVD, spontaneous vaginal delivery; TB, tuberculosis.

prophylactic antiviral treatment (Baggaley et al., 2006).

Early diagnosis and proper medical care could improve the quality of life for the mother and prevent fetal infection (Martí et al., 2007). Fighting the spread of the disease requires public awareness and well-organized national programs involving all health care providers. However, focusing on health education programs may offset the need for mandatory testing. Routine voluntary screening for HIV once every three to five years is justified on both clinical and economical grounds (Olagbuji et al., 2010). One time screening of the general population would also be cost effective (Al-Jabri et al., 2010). Saudi Arabia is financially capable of screening for these infections. HIV was recently included in the mandatory premarital screening test which provides screening for a

limited group of people. A larger screening program should be enforced in the health sector to determine the true prevalence of HIV in our community (David et al., 2005).

Conclusion

HIV is a major devastating health problem where late diagnosis often leads to a poor prognosis. This is further pronounced during pregnancy where both the lives of the mother and fetus are at risk. Early recognition and management of the disease by health care providers is the first step to deal with the situation. Public health officials should emphasize the importance of HIV awareness and screening. An early diagnosis integrated with intensified clinical care, obstetrical monitoring and nursing care is crucial to provide optimum treatment and a reduction of the rates of vertical transmission.

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Full Length Research Paper

Short-term combined exercise training improves the health of HIV-infected patients

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This study tested the benefits of combined aerobic and resistance exercise training (CARET) in HIV-infected individuals receiving antiretroviral therapy. Twenty-three human immunodeficiency virus (HIV)-infected men and women, predominantly of lower socioeconomic status (SES), were randomly assigned and completed 12 weeks of: (a) standard medical treatment plus CARET or (b) standard medical treatment only. At baseline and follow-up, immune functioning, metabolic variables, quality of life (QoL), physical characteristics, and physical fitness were measured. The control group showed a significant decrease in CD4+ T cell count (-16%, p<0.05), whereas the exercise group maintained a more stable count after the intervention (-3%, p=0.39). Furthermore, exercise participants showed significant improvements in waist circumference (-2%, p<0.05), fasting glucose (-16%, p<0.05), physical (+11%, p<0.03) and mental (+10%, p<0.02) QoL, estimated VO_{2max} (+21%, p<0.01), upper body strength (+15%, p<0.05), and lower body strength (+22%, p<0.05). Our 12-week, supervised, moderate-intensity CARET program resulted in more stable CD4 count and significant health improvements in HIV-infected individuals of lower SES.

Key words: Antiretroviral therapy, aerobic and resistance exercise training, immune functioning, quality of life.

INTRODUCTION

Each year, close to 50,000 Americans acquire human immunodeficiency virus (HIV), and recent reports indicate that Miami-Dade County, Florida has one of the highest number of new HIV cases in the country (Bureau of HIV/AIDS, 2011). Furthermore, women constitute the fastest growing group of new HIV/Acquired Immune Deficiency Syndrome (AIDS) diagnoses (Bokazhanova and Rutherford, 2006), and all groups that have a disproportionate lack of accessibility to health care, such as African Americans and Hispanics, have also been disproportionately affected by HIV/Acquired Immune Deficiency Syndrome (AIDS) (Fernandez et al., 2002). Today's standard of care of HIV-infected individuals is focused more on long-term adverse effects related to both infection and pharmacological treatment. However, despite the clear benefits, the previously unknown adverse effects of antiretroviral therapy (ART) have been

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emerging, representing a major health concern for this patient population.

Common but often mild undesirable effects of ART include disorders of the gastrointestinal tract (bloating, nausea, and diarrhea), nervous system (headache, pain/neuropathy, and fatigue), and integumentary system (rash and dry skin). Lipodystrophy, a visible condition characterized by abnormalities in the body's production, utilization, and distribution of fat can lead to increased risk for cardiovascular disease (CVD) and diabetes mellitus. Other serious but less prevalent adverse effects may include anemia, renal, liver, and mitochondrial toxicity, lactic acidosis, and osteopenia/osteoporosis (Calmy et al., 2007). In addition to adverse physical effects, patients receiving ART may also experience negative psychological responses such as agitation, confusion, anxiety, nightmares, mania, and depression (Horwath, 2011). Finally, these physical and psychological adverse reactions to ART may result in poor adherence to the treatment, which requires daily dosing at the appropriate times for the remainder of the patient's life. Ultimately, low adherence rates can cause drug resistance and consequently compromise a patient's immunity (Dieffenbach and Fauci, 2011).

Previous research has examined the impact of different forms of therapeutic exercise in HIV-infected individuals with aerobic exercise training representing the most widely used type of intervention. The research suggests that this patient population can achieve significant physical and psychological benefits from aerobic exercise after 12 weeks of moderate intensity training performed three times a week (Terry et al., 2006). More specifically, the benefits of any type of exercise in HIV-infected individuals may include improvements in body composition, functional capacity, muscular strength, lipid profile, cognitive function, depression, anxiety, and quality of life (QoL) (Bopp et al., 2003; Thoni et al., 2002; Yarasheski et al., 2011; Souza et al., 2008).

Given the rising prevalence and cost of lipodystrophy and metabolic consequences of ART and HIV itself, additional investigation of exercise training is justified. We examined the effect of a 12-week program of combined aerobic and resistance exercise training (CARET) on immune functioning, metabolic variables, QoL, physical characteristics, and physical fitness in a sample of persons with HIV on stable ART. The results of the study are intended to promote the use of CARET and its effects on our outcome variables of interest, leading to additional lines of research to address the multi-faceted problems of persons living with HIV.

MATERIALS AND METHODS

This study was a two-group, randomized controlled trial with assessments at two time points: (a) baseline or week 0 (±2 days; PRE) and (b) at the end of or during week 12 (±2 days; POST). Eligibility criteria included: (a) confirmed HIV infection with CD4+ T cell count ≥350 cells/mm^3, (b) men or women ≥18 years of age, (c) stable ART treatment in which therapy changes were not planned during the intervention, (d) a sedentary lifestyle, that is, failing to complete 30 min of exercise at least three times a week, as defined by American College of Sports Medicine (ACSM, 2006), and (e) a commitment to three weekly supervised exercise sessions for 12 weeks. Exclusion criteria included: (a) current opportunistic infection(s), (b) pregnancy, (c) use of lipid-lowering, insulin sensitizing, or hypoglycemic drugs, anabolic steroids, and/or growth hormone, or (d) any other medical condition or situation precluding adherence to and completion of the protocol.

The Institutional Review Board for human subjects at the University of Miami approved the study and its procedures. Potential participants (n=62) were recruited from the HIV Adult Outpatient Clinic at the University of Miami/Jackson Memorial Medical Center (UM/JMMC) and other local infectious disease clinics in Miami-Dade County between December, 2010 and August, 2011. Twenty-five participants failed the screening inclusion/exclusion criteria or they were eligible but never enrolled. Finally, 37 participants signed informed consent and Health Insurance Portability and Accountability Act (HIPAA) forms and enrolled in the study at baseline.

Subjects in the exercise (EX) group participated in a 12-week CARET intervention, consisting of three individual exercise sessions per week (Monday, Wednesday, and Friday) for a total of 36 sessions (Table 1). All sessions were 45 to 60 min long and contained different elements on various days: (1) endurance sessions utilizing a stationary treadmill or bicycle ergometer, (2) core exercises (back extension and abdominal crunches), and (3) ten strengthening exercises (leg press, leg extension, leg curl, chest press, lat pull, shoulder press, seated row, triceps press, biceps curl, and chest fly) consisting of one to three sets of 10 to 20 repetitions, performed on stacked-weight machines. All sessions were supervised by the study investigators. The control (CON) group did not participate in any supervised exercise as part of their 12 weeks in the study. CON participants were telephoned bi-weekly to maintain contact and promote their interest in the study.

The assessment protocol conducted at PRE and POST included: (a) immune functioning (CD4+ T cell count, CD4+/CD8+ ratio, HIV-RNA viral load), (b) metabolic variables (fasting glucose [FG] and lipids), (c) QoL (SF-36 Health Survey), (d) physical characteristics (body weight, body mass index [BMI], waist circumference [WAIST], and blood pressure), and (e) physical fitness (estimated VO_{2max} and one-repetition maximum [1RM] for upper and lower body strength).

Immune functioning

The number of CD4+ T lymphocytes was measured by flow cytometry (BD FACSCount, Bergen, NJ) using monoclonal antibodies, and plasma HIV-RNA was measured by the NASBA Nuclisens method (COBAS AmpliScreen, Roche, Quebec, Canada) with the lower limit of detection at 20 copies per milliliter.

Metabolic variables

Ten milliliters of venous blood were taken from the antecubital vein following an overnight fast of 10 to 12 h. Plasma glucose was measured by the glucose hexokinase method, and plasma levels of total cholesterol (T-Chol) and triglycerides (TG) were measured by enzymatic procedures. High-density lipoprotein cholesterol (HDL-C) was measured by selective inhibition and low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedwald equation:

LDL-C = T-Chol - (HDL-C - 0.20 × TG).

Table 1. Timeline for the combined aerobic and resistance exercise training (CARET) program.

Stage	Week	Session (week)	Type of exercise	Duration (min)	Intensity
Phase-in	0-2	3	Aerobic/Core/ Resistance	15-20/5-10 15-20	60% of HR_{max}/1RM
Step 1	3-6	1	Aerobic/Resistance	20-25/20-25	65% of HR_{max}/1RM
		1	Aerobic/Core	40-45/5-10	
		1	Aerobic/Resistance	5-10/40-45	
Step 2	7-9	1	Aerobic/Resistance	25-30/25-30	70% of HR_{max}/1RM
		1	Aerobic/Core	45-50/5-10	
		1	Aerobic/Resistance	5-10/45-50	
Step 3	10-12	1	Aerobic/Resistance	25-30/25-30	75% of HR_{max}/1RM
		1	Aerobic/Core	45-50/5-10	
		1	Aerobic/Resistance	5-10/45-50	

Very low-density lipoprotein cholesterol (VLDL-C) levels were calculated as the TG level divided by five, unless TG exceeded 400 mg/dl in which case VLDL-C was measured by enzymatic methods (Vitros 750 Analyzer, Johnson & Johnson, New York, NY).

QoL

QoL was assessed by the SF-36 Health Survey, which consists of 36 questions and evaluates eight scales: (a) physical functioning, (b) social functioning, (c) bodily pain, (d) general health perception, (e) vitality, (f) limitations due to emotional problems, (g) limitations due to physical health problems and (h) mental health. Each scale is scored 1 to 100, where a low score indicates perceived poor health and a high score represents perceived good health. Furthermore, the SF-36 is a generic measure that does not target a specific age, disease, or treatment group.

Physical characteristics

Weight and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively, to calculate BMI. WAIST was measured in inches at the narrowest circumference halfway between the lowest rib and the iliac crest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured to the nearest even digit by use of a random-zero sphygmomanometer (Mabis, IL, USA). Three readings were made with the subjects seated after they had rested for 5 min. The average of the second and third readings was used in the analysis.

Physical fitness

Submaximal testing for cardiorespiratory fitness was performed on a treadmill (Lifestyle Fitness 95T, Chicago, IL) using the Asymptomatic Cardiac Ischemia Pilot protocol. The subjects warmed up at 2 mph after which time of speed and/or incline were gradually increased until they reached 85% of age-predicted maximum heart rate. Heart rate was monitored with a chest-band transmitter and wristwatch display (Polar FT2, New York, NY). Each subject's treadmill time, speed, and incline were recorded, and estimated VO_{2max} was predicted from the following formula (Tamesis et al., 1993):

Estimated VO_{2max} (ml/kg/min) = (mph × 2.68) + (1.8 × 26.82 × mph × grade/100) + 3.5.

The protocol for 1RM testing followed the same American College of Sports Medicine (ACSM) guidelines (Hagerstwon, 2005) to determine maximum strength progress from a resistance training program from PRE to POST. More specifically, upper and lower body strength was assessed by chest press and leg press, respectively (Lifestyle Fitness, Chicago, IL). The subjects warmed up by completing a maximum of four trials of 10, 8, 6, and 3 repetitions with a rest period up to 4 min between trials. The initial weight was selected within the subject's perceived capacity (50 to 70% capacity), and resistance was progressively increased until the subject reached his/her maximum. The final maximum weight lifted successfully one time was recorded as the 1RM. Furthermore, all repetitions were performed at the same range of motion to ensure consistency between trials.

Statistical analysis

Data were analyzed using Statistical Package for Social Science (SPSS) 18 (IBM, Inc., Chicago, IL). Frequency and descriptive statistics were calculated on all variables. Independent sample t-tests were used to identify baseline differences for all variables between the CON and EX group. Repeated measures analyses of variance (ANOVA; 2 [group] × 2 [time]) were used to evaluate the effects for group, time, and the interaction between group and time for all outcome variables. An alpha level of 0.05 was used for all analyses.

RESULTS

At baseline, 18 EX and 19 CON subjects were enrolled in the study with 12 EX and 11 CON participants completing

Table 2. Socio-demographic characteristics of control and exercise participants.

Variable	Category	Control participants n (%)	Intervention participants n (%)
Years	Age	47.8 ± 4.5 (44, 59)	43.2 ± 9.5 (25, 57)
Gender	Female	4 (36.4)	5 (41.7)
	Male	7 (63.6)	7 (58.3)
Race	Non-Hispanic White	-	3 (25)
	African-American	11 (100)	6 (50)*
	Hispanic White	-	3 (25)
Marital status	Never Married	5 (45.5)	8 (66.7)
	Married	3 (27.3)	-
	Divorced	1 (9.1)	3 (25)
	Separated	1 (9.1)	1 (8.3)
Highest level of education	Up to high school	6 (54.5)	3 (24.9)
	Some Post High School Training	-	1 (8.3)
	College/Associate Degree	5 (45.5)	6 (50.0)
	College Graduate	-	2 (16.6)
Household Income ($)	Less than 5,000	6 (54.6)	2 (16.6)
	5,000-15,000	4 (36.4)	4 (33.3)
	15,000-30,000	1 (9.1)	4 (33.4)
	30,000-45,000	-	1 (8.3)
	45,000 or more	-	1 (8.3)
Other	Cups of Coffee/Day	1.3 ± 1.0	1.8 ± 1.9
	Days/Week Drinking Alcohol	1 ± 1.4	0.08 ± 0.3*
	Nightly hours of sleep	7 ± 2.5	7.7 ± 1.3

Values are mean ± standard deviation (minimum, maximum). *Significant difference between control and intervention subjects ($p<0.01$, unpaired t-test).

both PRE and POST evaluations (Table 2). Fourteen subjects (6 EX and 8 CON) dropped out of the study due to lack of interest or financial/family problems. Participants in the EX group attended an average of 29.4 (81%) supervised exercise sessions. The EX group (n=12) consisted of six African Americans, three non-Hispanic whites, and three Hispanic whites, while the CON group (n=11) consisted of all African Americans. The difference in proportion of African Americans between groups was significant (Table 1). Both groups were predominantly represented by individuals of lower socioeconomic status (SES), earning less than $15,000 per year. Finally, participants in both groups had been diagnosed with HIV for an average of more than 10 years (standard deviation (SD)±8.4, range 3 to 28), and all subjects were on stable ART for at least the prior 6 months.

Immune functioning

A significant main effects of time and the time × group interaction were found for CD4+ T cell count ($p=0.002$ and $p=0.03$, respectively; Figure 1) with the EX participants' values remaining stable and the CON participants' values decreasing from baseline (from 693.8 to 672.9 cells/mm^3 versus from 612.8 to 511.8 cells/mm^3). No significant main effect of time and time × group interactions were observed for CD4+/CD8+ ratio ($p=0.60$ and $p=0.49$) and HIV-RNA ($p=0.67$ and $p=0.29$; Figure 1).

Metabolic variables

A significant time × group interaction was found for FG ($p=0.048$) with the EX participants' values decreasing and

Table 3. Metabolic variables and physical characteristics of control and exercise participants at baseline and follow-up.

Variable	Control participants (CON)		Intervention participants (EX)	
	Pre	Post	Pre	Post
T-Chol (mg/dl)	191.9 ± 43.0	184.9 ± 49.6	201.7 ± 48.5	195.5 ± 48.0
LDL-C (mg/dl)	107.4 ± 32.1	101.9 ± 35.8	118.2 ± 37.3	111.5 ± 35.2
HDL-C (mg/dl)	58.4 ± 16.5	59.2 ± 14.7	49.9 ± 16.8	50.7 ± 18.7
VLDL-C (mg/dl)	26.0 ± 13.1	23.8 ± 17.4	33.6 ± 19.3	32.4 ± 24.5
T-Chol/HDL	3.5 ± 1.1	3.3 ± 1.3	4.3 ± 1.8	4.2 ± 1.6
TG (mg/dl)	129.1 ± 66.8	119.6 ± 87.1	170.8 ± 105.0	157.9 ± 93.7
FG (mg/dl)	79.7 ± 10.3	83.1 ± 7.4	92.7 ± 16.4	80.7 ± 10.0†
BW (lbs)	195.5 ± 41.3	196.5 ± 46.5	209.9 ± 64.6	209.9 ± 63.9
BMI	30.8 ± 6.6	31.1 ± 7.5	33.6 ± 10.2	33.6 ± 10.1
WAIST (in)	39.1 ± 7.1	39.5 ± 7.5	41.2 ± 8.0	40.4 ± 7.7†
SBP (mmHg)	132 ± 16	124 ± 17*	119 ± 9†	120 ± 6
DBP (mmHg)	80 ± 10	81 ± 9	81 ± 5	77 ± 11

Values are mean ± standard deviation (minimum, maximum). T-Chol: Total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; VLDL-C: very-low density lipoprotein cholesterol; TG: triglycerides; FG: fasting glucose; BW: body weight; BMI: body mass index; WAIST: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.05$, ANOVA). †Significantly different from CON at the same time point ($p<0.05$, ANOVA)

Table 4. The SF-36 of control and exercise participants at baseline and follow-up.

Variable	Control participants (CON)		Intervention participants (EX)	
	Pre	Post	Pre	Post
Physical functioning	77.2 ± 30.1	63.3 ± 41.6	78.3 ± 31.4	87.1 ± 16.8*
Role - Physical	67.0 ± 25.7	60.8 ± 34.5	73.9 ± 40.7	77.6 ± 23.3
General health	62.5 ± 24.7	60.3 ± 20.6	75.0 ± 28.1	76.4 ± 24.7
Vitality	56.3 ± 25.5	54.5 ± 28.1	69.8 ± 27.5	74.5 ± 18.6
Social functioning	84.7 ± 24.0	86.1 ± 26.1	71.9 ± 39.2	81.3 ± 20.9
Role - Emotional	70.5 ± 29.7	65.1 ± 30.5	84.7 ± 26.8.2	91.7 ± 13.3
Mental health	75.0 ± 22.7	65.5 ± 23.5	79.2 ± 23.7	87.1 ± 10.3*
Bodily pain	62.5 ± 29.5	61.5 ± 30.6	88.8 ± 11.8	77.9 ± 16.7

Values are mean ± standard deviation (minimum, maximum). PRE: Baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from CON at the same time point ($p<0.05$, ANOVA).

the CON group's values increasing from baseline (from 92.7 to 80.7 versus from 79.7 to 83.1, respectively; Table 3). Repeated measures ANOVAs for the serum lipid profile indicated no main effects for either time or time × group interactions for T-Chol (p=0.17 and p=0.93), LDL-C (p=0.14 and p=0.89), HDL-C (p=0.64 and p=0.99), T-Chol/HDL-C ratio (p=0.20 and p=0.96), and TG (p=0.40 and p=0.90; Table 2).

QoL

Significant time × group interactions were observed for the physical functioning (p=0.03) and mental health (p=0.02) scales on the SF-36 with the EX participants' values improving (+8.8 and +7.5 points, respectively) and the CON participants' values worsening (-14 and -9.5 points, respectively) from baseline (Table 4).

Physical fitness

Significant main effects of time and time × group interactions were found for VO_{2max} (p=0.001 and p=0.002, respectively; Figure 2) with the EX participants' values increasing (+4.7 ml/kg/min) and the CON participant's

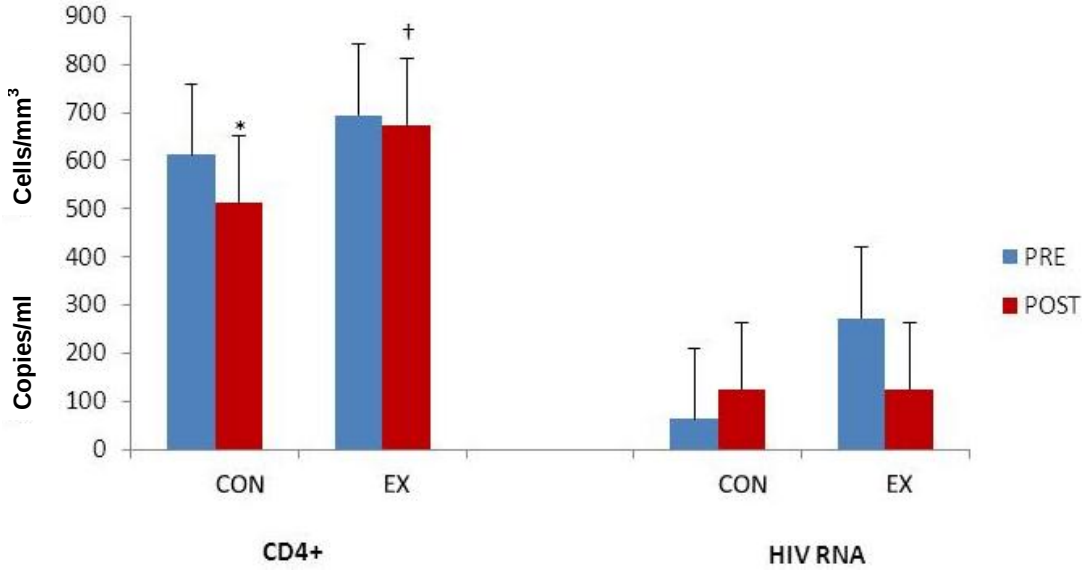

Figure 1. Changes in CD4+ cell count and HIV-RNA viral load in control and exercise participants at baseline and follow-up. CD4+: CD4+ T cell count; HIV RNA: HIV-RNA viral load; CON: control participants; EX: exercise participants; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.05$, ANOVA). †Significantly different from CON at the same time point ($p<0.01$, ANOVA).

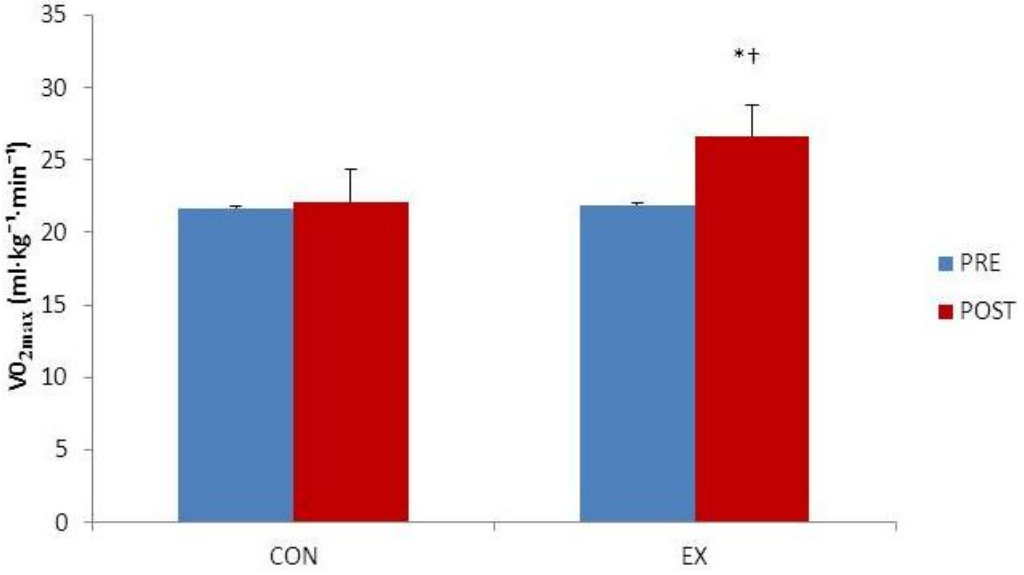

Figure 2. Changes in estimated maximum oxygen consumption (VO_{2max}) in control and exercise participants at baseline and follow-up. Estimated VO_{2max}: Estimated maximal oxygen consumption; CON: Control participants; EX: exercise participants; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.01$, ANOVA). †Significantly different from CON at the same time point ($p<0.01$, ANOVA).

values remaining the same (+0.4 ml/kg/min). Furthermore, significant main effects of time and time × group interactions were found for 1RM bench press for upper body strength ($p=0.003$ and $p=0.018$, respectively) and 1RM leg press for lower body strength ($p=0.01$ and $p=0.03$, respectively) with the EX participants' values

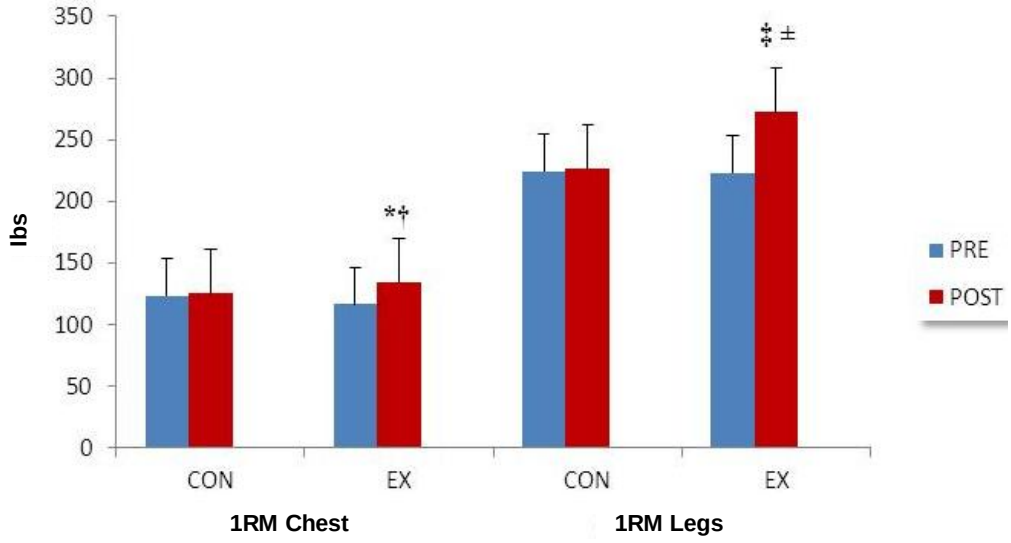

Figure 3. Changes in one-repetition maximum (1RM) for chest and legs in control and exercise participants at baseline and follow-up. LBS: pounds; 1RM CHEST: 1 repetition maximum for chest press; 1RM LEGS: 1 repetition maximum for leg press; CON: control participants; EX: exercise participants; PRE: baseline evaluation; POST: 12-week follow-up evaluation. *Significantly different from PRE within the same group ($p<0.05$, ANOVA). †Significantly different from CON at the same time point ($p<0.01$, ANOVA). ‡Significantly different from PRE within the same group ($p<0.05$, ANOVA). ±Significantly different from CON at the same time point ($p<0.05$, ANOVA).

improving (+17.9 and +49.1 lbs, respectively) and the CON participant's values remaining the same from baseline (+2.3 lbs and +1.9, respectively; Figure 3).

DISCUSSION

Thirty-eight percent of our subjects withdrew from the study, which is similar to the findings of a meta-analysis on aerobic exercise and HIV/AIDS in which six studies reported drop-out rates higher than 20% and two higher than 50% (Nixon et al., 2002). Furthermore, our EX participants achieved a higher completion rate (81%), compared to similar exercise intervention trials for this patient population (70 and 78%, respectively) (Fairfield et al., 2001; Hand et al., 2008).

Immunological markers not only give prognostic information on HIV, but they are also linked to HIV-related illness and mortality. Recent clinical trials have consistently shown no significant improvements in CD4+ T cell count and/or HIV-RNA levels after moderate-intensity training (Terry et al., 2006; Smith et al., 2001). Our result shows that the EX participants demonstrated a more stable CD4+ T cell count from baseline of -3%, while the CON group experienced a significant reduction of -16% after 12 weeks. Furthermore, the drop in CD4+ T cell count was observed in eight (73%) CON individuals compared to only four (33%) EX participants. Although EX participants had no significant increase in CD4+ T cell count, the fact that the group mean level remained stable is a positive finding. Favorable results were also found in viral load with only one EX participant (8%) having higher HIV-RNA viral load at 12 weeks follow-up, compared to four CON participants (36%) demonstrating a higher viral load. Finally, decreased HIV-RNA viral load, together with stable CD4+ count in the EX participants, represent more favorable prognoses and can attenuate progression to symptomatic disease. Two possibilities may explain the immunological responses of our intervention. Our trial included people of lower SES facing greater life-stress, and thus the exercise intervention may have indirectly caused a normalization of stress-induced CD4+ T cell count depletion. A similar result was reported in a study performed before the ART era in which a 10-week aerobic exercise program showed an increase of CD4+ T cell count in individuals with lower SES levels (Laperriere et al., 1994). Another possible explanation is the social support that our exercise intervention provided, which may have caused better adherence to ART and subsequently improved the immunological profile of the EX group. Similar results in social support and enhanced adherence to ART have been previously demonstrated (Van et al., 2005).

Regarding metabolic changes, both groups had normal baseline FG levels, but demonstrated opposite trends at 12-week follow-up. While the EX participants experienced a 13% reduction, the CON individuals showed a 4% increase in FG levels. This finding contrasts with the

results of a previous study in which a 12-week exercise intervention, combined with a diet, did not improve high FG levels in HIV-infected individuals receiving ART (Terry et al., 2006). A similar prevalence of metabolic syndrome has been reported for both HIV-infected and the general populations (De et al., 2008). In our study, HIV-infected individuals did not present with fasting hyperglycemia. However, a recent study suggested that higher values of FG (90 to 94 mg/dl), similar to the values observed in our EX group and still considered in the normal range, are associated with a significantly increased risk of type 2 diabetes (Nichols et al., 2008). Our results suggest that a 12-week CARET intervention can improve FG in euglycemic HIV patients and thus reduce the future risk of hyperglycemia and diabetes.

Past research has shown favorable changes in serum lipids after 12 weeks of training in patients with dyslipidemia not receiving ART (Halbert et al., 1999). Despite a more adverse metabolic lipid profile observed in the EX group at baseline, CARET did not result in significant changes in plasma lipid levels. Overall, our findings are consistent with two other studies performed in HIV-infected individuals receiving ART. Terry et al. (2006) showed no significant improvements in TG, T-Chol, and HDL-C after 12 weeks of aerobic exercise, while other investigators failed to show significant reductions in serum TG after 12 months of aerobic exercise (Birk et al., 2002). In contrast, Thoni et al. (2002) did find significant improvements in T-Chol, TG, and HDL-C (-23, -43, and +6%, respectively) after a 16-week aerobic training program in 17 lipodystrophic and dyslipidemic HIV patients. The lack of changes in serum lipids in our subjects may be related to the fact that subjects did not present with dyslipidemia at baseline and/or that the intervention was not of sufficient length.

In addition to negative physical changes, HIV-infected patients receiving ART can also experience psychological symptoms, and fatigue, depression, and anxiety represent the most common ones in this population. Our EX participants reported significant improvements in both physical and mental QoL scales (16 and 9%, respectively), while the CON participants had lower scores on the same scales (-18 and -12%, respectively). This indicates that the EX participants reported improvements in performing daily activities such as bathing, dressing, walking, climbing stairs, and carrying groceries, which are captured in the physical QoL scale. Furthermore, higher mental QoL scores observed in the EX group indicate improved mental health with CARET and lower risk of depression (Stoll et al., 2001). Interestingly, our intervention resulted in a positive trend in seven of the eight scales, while the CON participants exhibited negative trends in the same SF-36 scales. Our survey results may also explain the more stable CD4+ T cell count found in EX subjects, as impaired mental health status has been linked with decreased CD4+ T cell values (Leserman et al., 1999).

All physical variables were similar between groups initially with the exception of SBP, which was higher in the CON group compared to the EX group. This difference may be explained by higher rates of hypertension in African Americans and the fact that the CON group was entirely African American. This group experienced a significant reduction in SBP at the end of 12 weeks. Since no alterations in antihypertensive medications were made during the trial, the reduction in SBP in the CON group could have been due to variance (or error) in measurement.

Despite no significant changes in body weight in either group, the EX group experienced a reduction and the CON group an increase in their WAIST. Since HIV-infected individuals receiving ART are at risk for greater visceral fat accumulation, they represent a population more likely to have metabolic abnormalities associated with CVD and diabetes (Brown et al., 2010). Therefore, significant reductions in WAIST in the EX group may be a marker for decreased risk of metabolic diseases associated with abdominal obesity.

The EX group also improved their estimated VO_{2max}, an important measure of aerobic capacity related to health and longevity. Generally, aerobic fitness declines at approximately 1% per year in healthy individuals beyond the age of 25 (Rosen et al., 1998) and even more in adults with chronic diseases (Palella et al., 1998). More specifically, conditioned HIV-infected individuals may have up to 9% lower VO_{2max} values compared to age-matched healthy individuals (Johnson et al., 1990). These decrements may subsequently translate into lower endurance, quicker fatigue, and reduced independence during daily life activities in sedentary individuals. Abnormalities specific to reduced aerobic capacity in the HIV-infected population include decreased lactate threshold and reduced peripheral muscle oxygen utilization during exercise. These problems are often related to mitochondrial toxicity (Cade et al., 2003) caused by nucleoside reverse transcriptase inhibitors (NRTI), the cornerstone of ART therapy. Low estimated VO_{2max} values were observed in both CON and EX groups at baseline, signifying low functional aerobic capacity in this sample. This impairment is consistent with the finding that sedentary HIV-infected individuals may have estimated VO_{2max} values below 30 ml/kg/min with values of 24 to 44% below age-predicted norms (Keyser et al., 2000). However, despite continued ART therapy in both groups, the EX group was able to achieve a significant 21% improvement in estimated VO_{2max}, while the CON group showed no change. In contrast to our results, others have found non-significant 9 to 10% increases in VO_{2max} following a similar combined training protocol after 12 and 16 weeks in HIV-infected individuals (Smith et al., 2001; Robinson et al., 2007). Our results are more closely related to an older study (Robinson et al., 1992)

conducted in 37 male HIV-infected individuals in which VO_{2max} improved 17% after 12 weeks of aerobic training. Since reduced aerobic capacity can be associated with lower CD4+ T Cell count and faster progression to AIDS, improved cardiorespiratory fitness from our CARET intervention may translate into more stable and favorable health outcomes in HIV-infected individuals.

Muscular strength is another component of physical fitness relevant to health and longevity. In our trial, the EX compared to CON group achieved significant improvements in upper (15%) and lower (21%) body strength. Increases in both upper and lower body strength are associated with improved functional capacity, reduced risk of falls, and a lower incidence of hip fractures in the elderly (Robinson et al., 1987). Thus, our findings of improved musculoskeletal strength may have significant implications for better independence later in life. Despite our shorter intervention length, the strength gains of this study were similar to those of a 16-week CARET intervention (Robinson et al., 2007) using participants similar in age to ours. Their trial also showed an 18% increase in 1RM for four upper and three lower body resistance exercises. Similar to our findings, Yarasheski et al. (2001) found larger improvements in lower body, compared to upper body, strength in 18 HIV-infected individuals. Smaller increases in upper body strength can be attributed to NRTI medications, which can cause peripheral neuropathy and limited ability to recruit motor nerves in the upper body musculature (Fichtenbaum et al., 1995). This physiological limitation, associated with the side effects of NRTI, signifies the importance of performing more upper body training for persons living with HIV.

LIMITATIONS

Several limitations of this study should be noted. The small sample size represents a major limitation. Despite high compliance with the exercise protocol, we did observe a high attrition rate. African Americans had a higher attrition rate in the EX group and non-Hispanic whites and Hispanics withdrew at a higher rate in CON group. Each control subject had an opportunity to undergo the same exercise protocol after completing the study. However, all non-African Americans assigned to CON group discontinued the study, which explains our randomization bias.

The subjects in this study used laboratory analyses from the clinic, where they received their usual care. Therefore, the study protocol schedule and the participants' blood draw appointments were not always perfectly matched for every participant. Specifically, the baseline blood draw appointments may have occurred a few days before or after the beginning of the exercise intervention, and the same problem may have occurred with the 12-week follow-up appointments for both groups.

Finally, we had no formal protocol to check medication compliance. Based upon regular communication with each participant, we could only speculate that adherence to the ART regimen occurred. However, several participants from both groups reported a single short gap (3 to 5 days) in obtaining their medications from the pharmacy, which may have affected their immunological response.

Conclusions

In this study, it was found out that a 12-week, supervised, moderate-intensity CARET program resulted in more favorable clinical findings in immunological markers in HIV-infected individuals of lower SES compared to their non-exercising counterparts. This is an important finding, recognizing that HIV patients of lower SES have greater susceptibility to disease progression and premature mortality (Cunningham et al., 2005). The results indicate that the same exercise protocol can result in other health improvements, such as reductions in FG and WAIST and improvements in physical and mental QoL, aerobic fitness, and muscular strength. Given the promising results of our study, future trials should continue to utilize combined aerobic and resistance exercise, as a more health-promoting form of training in this patient population (Lindegaard et al., 2008). Finally, longer exercise protocols (>3 months) are needed to more conclusively determine the link between increased physical fitness and the immunological functioning of HIV patients receiving stable ART.

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Full Length Research Paper

Hepatitis A vaccination among human immuno-deficiency virus (HIV)-infected adults: Current evidence and unanswered questions

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Hepatitis A virus (HAV) infection is common, can cause significant morbidity and mortality, and the prevalence may be higher in populations infected or at risk for human immunodeficiency virus (HIV). Immunization with HAV vaccine is recommended for HIV-infected individuals, particularly men who have sex with men, injection drug users, hemophiliacs, those with chronic liver disease, and international travelers without immunity to HAV. HAV vaccination is well-tolerated among HIV-infected individuals and is immunogenic, particularly among those with higher $CD4^+$ cell counts. HIV-infected individuals have lower seroconversion rates and antibody concentrations in response to vaccination. However, protection against HAV as measured by HAV antibody levels is achieved for most cases. Adverse event rates are similar among those with and without HIV infection, and HAV vaccine does not have a marked impact on HIV-1 ribonucleic acid (RNA) levels, progression to acquired immune deficiency syndrome (AIDS), or $CD4^+$ cell counts. Areas of controversy remain, including timing of vaccination relative to initiation of antiretroviral therapy, rate and impact of antibody decline over time, need for booster immunizations, and the benefit of follow-up antibody titer monitoring.

Key words: Hepatitis A virus, human immunodeficiency virus (HIV), vaccination, vaccine.

INTRODUCTION

Acute viral hepatitis is one of the most common infectious diseases, and hepatitis A virus (HAV) is the most frequent form of acute viral hepatitis throughout the world (Koff, 1998). There is an estimated 1.5 million clinical cases of HAV infection reported worldwide annually, a figure that greatly underestimates the true incidence of infection (Martin et al., 2006). In the United States, HAV is one of the most frequent of the reportable diseases (Wasley et al., 2008), however, since the adoption of routine HAV vaccination, the United States and other countries have seen a dramatic decline in HAV infections and HAV-related mortality (Daniels et al., 2009; Klevens et al., 2010; Vogt et al., 2008; Wasley et al., 2005, 2006, 2008; Zhou et al., 2007). Despite this decline in incidence, HAV remains an important and preventable cause of morbidity and mortality with an estimated 25,000 cases per year in the United States (Daniels et al., 2009; Martin et al., 2006; Zhou et al., 2007), over 17,000 confirmed cases per year (based on 2009 data) in the European Union (European Centre for Disease Prevention and Control, 2011), and over 35,000 deaths per year globally (World Health Organization (WHO), 2012).

The prevalence of HAV infection in populations infected or at risk for HIV is high (Cotter et al., 2003; Fonquernie et al., 2001; O'Riordan et al., 2007; Sun et al., 2009; Villano et al., 1997), and has been estimated at 40 to 70% in resource-rich nations (Laurence, 2005) and nearly

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Abbreviations: ALT, Alamine aminotransferase; **HAART,** highly active antiretroviral therapy; **HAV,** hepatitis A virus; **IDUs,** injection drug users; **MSM,** men who have sex with men.

100% in developing countries (Jacobsen et al., 2010). A French study in the late 1990s reported an annual incidence of HAV infection of 6% among HIV-infected individuals (Fonquernie et al., 2001). Others have estimated the annual incidence of HAV among HIV-infected individuals as high as 1.5% (Wallace et al., 1998) although these estimates were generated before the vaccine-associated decline in HAV infection. Despite dramatic reductions overall, relatively high disease rates persist among adult males less than 40 years of age (Wasley et al., 2005), and the proportion of cases among men who have sex with men (MSM) is increasing (Wasley et al., 2008), making HAV infection particularly relevant to HIV-infected individuals. The US Department of Health and Human Resources guidelines for opportunistic infections recommend HAV vaccination for seronegative HIV-infected individuals, particularly MSM, injection drug users (IDUs), hemophiliacs, those with chronic liver disease including hepatitis B and C, and international travelers (Kaplan et al., 2009).

HAV vaccination rates are very low across the US (Laurence, 2005; Tedaldi et al., 2004). A study of multiple sites across the U.S. demonstrated low vaccination rates even among HIV-infected MSM (Hoover et al., 2012). Additional studies are needed to better understand the factors contributing to these low vaccination rates even among high-risk patients.

The course of acute HAV infection among HIV-infected individuals is variable and may not differ from the course of those without HIV (Dabrowska et al., 2011; Wallace et al., 1998). Data are limited, however the possibility of more severe and prolonged disease in those with HIV has been raised (Costa-Mattioli et al., 2002; Fonquernie et al., 2001; Ida et al., 2002).

HAV infection in HIV-infected individuals may in some cases be associated with longer time to normalization of alanine aminotransferase (ALT) levels (Fonquernie et al., 2001) and more prolonged HAV viremia compared with healthy adults (Costa-Mattioli et al., 2002; Ida et al., 2002). Furthermore, HAV infection may impact HIV disease by increasing HIV replication, at least in part, to associated disruptions in antiretroviral therapy; however this is based on limited data and case reports (Fonquernie et al., 2001; Ridolfo et al., 2000; Wallace et al., 1998), and a more recent case series suggested that it occurred even among those who did not disrupt their antiretroviral therapy (Gallego et al., 2011). Chronic hepatitis B and C infections are common among HIV-infected individuals (Sherman et al., 2002; Shire et al., 2004) and morbidity and mortality due to chronic liver disease is increasing among those with HIV (Bica et al., 2001; Jain et al., 2003). These chronic liver conditions may predispose HIV-infected patients to fulminant hepatic injury when infected with HAV (Keeffe, 1995; Vento et al., 1998). Despite the higher rates and potentially more severe or prolonged course of HAV among HIV-infected individuals, vaccination rates remain low with estimates ranging from 6 to 54% (Hoover et al., 2012; Overton et al., 2007; Tedaldi et al., 2004; Winnock et al., 2011).

METHODOLOGY

We searched for articles using Pubmed. Search terms included HIV, hepatitis A, and vaccination and vaccine. Approximately 500 articles were found in response to a joint search of both HIV and hepatitis A. We reviewed recent U.S. and European HIV guidelines and Advisory Committee on Immunization Practices (ACIP) guidelines. In addition, we reviewed bibliographies from relevant articles for other potential studies.

BRIEF HISTORY OF HAV VACCINATION IN THE UNITED STATES

HAV was first isolated in 1973 (Feinstone et al., 1973), fo-llowed soon after by development of the prototype vaccine and then other vaccines (Andre et al., 1992; Dagan et al., 1999; Loutan et al., 1994, 2007; Nalin et al., 1993; Provost et al., 1978). Large-scale clinical trials were then performed to demonstrate the efficacy and safety of HAV vaccines (Clemens et al., 1995; Innis et al., 1994; Werzberger et al., 1992). By 1995, a safe and effective vaccine was commercially available (Andre et al., 1992; Dienstag, 2008). Two single-antigen inactivated HAV vaccines are commonly used: HAVRIX (GlaxoSmithKline Biologicals, Rixensart, Belgium) with 2 doses at 0 and 6 to 12 months, and VAQTA (Merck & Company, Inc., Whitehouse Station, New Jersey) (Wasley et al., 2006) with 2 doses at 0 and 6 to 18 months (Wasley et al., 2006). Both are of similar efficacy and safety (Ashur et al., 1999; Orr et al., 2006). There is also a combination vaccine (TWINRIX, GlaxoSmithKline Biologicals, Rixensart, Belgium) which contains inactivated HAV and recombinant hepatitis B antigen (Wasley et al., 2006) with 3 doses at 0, 1, and 6 months (Wasley et al., 2006). However, the HAV dose in the combination vaccine is only 720 Enzyme-linked immuno-sorbent assay (ELISA) units, which is half the dose of the single-antigen inactivated HAV vaccines (Wasley et al., 2006).

Initially, HAV vaccination was targeted at groups and individuals at increased risk of HAV or its consequences such as travelers to endemic areas, MSM, injection drug users (IDUs), and persons with clotting factor disorders or chronic liver disease (Advisory Committee on Immunization Practices (ACIP), 1996). Nevertheless, vaccination rates among these groups remained low (Arguedas et al., 2002; Bialek et al., 2011; Campbell et al., 2007; Carey et al., 2005; Diamond et al., 2003; Friedman et al., 2000; Hoover et al., 2012; Jin et al., 2004; O'Riordan et al., 2007; Shim et al., 2005; Siconolfi et al., 2009; Vong et al., 2005) despite continued outbreaks and higher rates of HAV infection among MSM (Corey and Holmes, 1980; Girardi et al., 2010; Centers for Disease Control and Prevention (CDC), 1998; Kahn,

2002; O'Riordan et al., 2007; Ochnio et al., 2001; Schomer et al., 1992; Stokes et al., 1997; Tortajada et al., 2012) and injection drug users (Ochnio et al., 2001; Quaglio et al., 2006; Villano et al., 1997), and even after reports of fulminant hepatitis due to HAV in patients with chronic liver disease (Keeffe, 1995; Vento et al., 1998).

A stepwise approach was taken to expand HAV vaccine recommendations in children. In 1996, routine vaccination was recommended for children over 2 years of age living in endemic communities (ACIP, 1996). This was expanded to include children living in 17 states with elevated HAV rates in 1999 (ACIP, 1999) and, in 2006, to all children aged 12 to 23 months nationwide (Fiore et al., 2006). Introduction of routine childhood HAV immunezation has led to a reduction in HAV incidence among adults (Averhoff et al., 2001; Dagan et al., 2005; Klevens et al., 2011; Samandari et al., 2004) and contributed to the overall decline in national HAV incidence rates (Daniels et al., 2009; Samandari et al., 2004; Wasley et al., 2006; Wasley et al., 2005), as well as a decline in the overall age-adjusted HAV mortality rates (Vogt et al., 2008).

RESPONSE RATES TO HAV VACCINATION

The protective effect of HAV vaccination, typically measured as long-term persistence of vaccine-induced anti-HAV antibodies, has been established in numerous studies of vaccinated populations including infants, children, and adults (including the elderly) (Briem and Safary, 1994; Chan et al., 1999; D'Acremont et al., 2006; Dagan et al., 2000; Fan et al., 1998; Innis et al., 1994; Iwarson et al., 2002; Orr et al., 2006; Piazza et al., 1999; ACIP, 1996; Troisi et al., 1997; Van Damme et al., 2003; Van Der Wielen et al., 2007; Van Herck et al., 2001; Van Herck et al., 2004; Werzberger et al., 1992; Werzberger et al., 2002). Although studies vary, most defined a serum antibody level of 20 mIU/ml as the minimum needed to define seroconversion or protective immunity (Kourkounti et al., 2012; Tilzey et al., 1996; Weinberg et al., 2006). Early clinical trials before 1995 used a 3-dose series with HAVRIX while most recent studies have documented the efficacy of the current universally accepted two-dose schedule (Van Damme et al., 2003). Among immune competent individuals, a 2-dose vaccine series produces protective HAV antibody levels in 95 to 100% of individuals (Levy et al., 1998).

There are a number of reasons to expect a lower response rate to HAV vaccination in HIV-infected individuals compared with HIV-uninfected populations. First, the immunogenicity of most vaccines is decreased among immune compromised individuals (Pirofski et al., 1998) including those with HIV (Bekker et al., 2006; Rivas et al., 2007) and second, HIV-infected populations commonly have habits or conditions that may suppress the response to vaccination such as alcohol and tobacco use, injection drug use, malnutrition and hepatitis C virus coinfection (Laurence, 1997).

Response rates to HAV vaccination among HIV-infected individuals range between ~46 to 97% (Armstrong et al., 2010; Crisinel et al., 2012; Kemper et al., 2003; Kourkounti et al., 2012; Loutan et al., 2007; Neilsen et al., 1997; Overton et al., 2007; Santagostino et al., 1994; Siberry et al., 2008; Tilzey et al., 1996; Tseng et al., 2012; Valdez et al., 2000; Wallace et al., 2004; Weissman et al., 2006). These rates vary in part due to differences in patient characteristics including age and $CD4^+$ cell count, as well as vaccination schedule and antibody assay used to measure the response (Loutan et al., 2007; Siberry et al., 2008; Tseng et al., 2012). Despite the relatively large number of studies performed, most had small sample sizes making definitive conclusions regarding vaccine efficacy difficult. A meta-analysis including 8 studies with a combined total of 458 individuals found an overall HAV vaccine response rate among HIV-infected individuals of 64% (Shire et al., 2006). Several studies in the era before highly active antiretroviral therapy (HAART) demonstrated lower seroconversion rates among HIV-infected individuals compared with HIV-uninfected individuals (Hess et al., 1995; Neilsen et al., 1997; Santagostino et al., 1994; Tilzey et al., 1996). Direct comparison studies have found seroconversion rates of 76 to 94% versus 100% among HIV-infected and uninfected individuals, respectively (Neilsen et al., 1997; Tilzey et al., 1996; Wallace et al., 2004). One study conducted among patients with hemophilia prior to HAART reported an overall vaccine response rate of 76% at 1 year in HIV-infected individuals versus 100% in controls, with only 40% response among subjects with AIDS (Santagostino et al., 1994). In general, anti-HAV titers in HIV-infected individuals are lower by a factor of ~3 to 10 compared with HIV-uninfected vaccines (Neilsen et al., 1997; Overton et al., 2007; Tilzey et al., 1996; Wallace et al., 2004). Despite lower seroconversion rates and antibody concentrations in HIV-infected individuals, protection against HAV as measured by HAV antibody levels is achieved for most.

FACTORS ASSOCIATED WITH RESPONSE TO HAV VACCINATION AMONG HIV-INFECTED INDIVIDUALS

HIV-infected individuals with nearly normal $CD4^+$ cell counts have similar vaccine response rates but lower antibody levels compared to HIV-uninfected vaccines (Wasley et al., 2006) while patients with more advanced HIV infection have lower response rates and lower antibody levels (Loutan et al., 2007; Rigaud et al., 2008; Wasley et al., 2006). In general, high $CD4^+$ cell counts at the time of vaccination are associated with better seroconversion rates and higher mean anti-HAV antibody titers (Crisinel et al., 2012; Crum-Cianflone et al., 2011; Kemper et al., 2003; Lederman et al., 2003; Neilsen et

al., 1997; Siberry et al., 2008; Valdez et al., 2000; Weinberg et al., 2012; Weissman et al., 2006) (Table 1). One study of 214 vaccinated individuals reported that 80% of patients with a $CD4^+$ cell count > 500 cells/mm^3 at the time of vaccination responded versus < 10% of those with a $CD4^+$ cell count < 50 cells/mm^3 (Rimland et al., 2005). A randomized controlled trial suggested that patients with a $CD4^+$ count between 350 and 500 cells/mm^3 had greater vaccine response rates than those with $CD4^+$ counts between 200 and 350, however this did not reach statistical significance (Launay et al., 2008).

Although the effect of $CD4^+$ cell count on vaccine response rates has been examined in many studies, relatively few have investigated the impact of HIV-1 viral load on seroconversion. One study found that HAV vaccine responders had a lower HIV-1 viral load compared with non-responders (6,104 versus 26,267 copies/ml, $p = 0.03$) in unadjusted analyses, however this association did not persist after controlling for other factors (Weissman et al., 2006). In contrast, another study (N = 268) found that antibody response rates among those with an HIV-1 viral load level below 1000 copies/ml were 2.25 times higher than response rates among those with an HIV-1 viral load above 1000 copies ($p = 0.01$) (Overton et al., 2007). Most recently, a study of HIV-infected women found an association between HIV-1 viral load < 400 copies/ml and likelihood of HAV antibody response to vaccination (OR 1.7, $p = 0.04$) (Weinberg et al., 2012). Multivariate analyses among children demonstrated an association between undetectable HIV-1 viral load and higher anti-HAV antibody titers (Weinberg et al., 2006, 2009). A study of 130 HIV-infected adults demonstrated that lower HIV-1 viral load values over time were associated with maintaining higher mean anti-HAV antibody titers (Crum-Cianflone et al., 2011).

In addition to HIV disease-specific factors, other characteristics may impact response rates to HAV vaccination among HIV-infected individuals. For example, tobacco use, which is common among HIV-infected populations (Cockerham et al., 2010), is associated with poorer response rates to hepatitis B vaccine among immune competent individuals (Winter et al., 1994). Although data on the impact of smoking on HAV vaccine response rates among HIV-infected individuals is limited, one trial of 2 versus 3 dose HAV vaccination schedules among HIV-infected individuals did find that smoking was associated with a poorer response to HAV vaccine (Launay et al., 2008). Questions remain regarding other factors that may impact response as well, such as nutritional status, co-infections, genetic predisposition, and many others.

HAV VACCINE SAFETY

Safety among HIV-uninfected individuals

Cumulative global experiences from several hundred million doses have demonstrated that the overall safety profile of hepatitis A vaccine has been excellent (Demicheli and Tiberti, 2003; WHO, 2012). Data from worldwide pre-licensure clinical studies of over 60,000 individuals did not definitively attribute any serious adverse events to HAV vaccine (Fiore et al., 2006; ACIP, 1996). Among adults, the most frequent side effects were tenderness at the injection site (56%), headache (14%), and malaise (7%), with an incidence similar to HBV vaccine (ACIP, 1996). Another study found the most frequent side effects after vaccination were tenderness (53%), pain (51%), warmth (17%) at the injection site, and headache (16%) (Fiore et al., 2006).

Reports of rare serious adverse events included anaphylaxis, Guillain-Barre syndrome, transverse myelitis, encephalitits, and multiple sclerosis (ACIP, 1999). However, regarding these serious adverse events for which background incidence data were known, the rates among vaccine recipients were not higher than expected for an unvaccinated population (ACIP, 1999). The initial 2-year safety review by the Vaccine Adverse Event Reporting System reported few unexpected HAV vaccine associated serious events despite the use of at least a million vaccines doses in the US, and stated that it reaffirmed the safety of the HAV vaccine in the general po-pulation (Niu et al., 1998). The safety of the vaccine is continually assessed through ongoing data monitoring from the Vaccine Adverse Event Reporting System and it is excellent (Fiore et al., 2006).

HAV vaccine side-effects among HIV-infected individuals

HAV vaccines have typically been well-tolerated among HIV-infected individuals with common mild local reactions but rare systemic reactions. A study of MSM reported local tenderness as the most common side-effect, occurring in 10% of HIV-infected versus 9% of HIV-uninfected men (Neilsen et al., 1997). Mild systemic symptoms such as headache, rash, nausea, lightheadedness, and myalgias were reported by 33% of HIV-infected and 15% of HIV-uninfected individuals (Neilsen et al., 1997). A study of 90 HIV-infected and 90 HIV-uninfected individuals found rates of systemic adverse events; predominantly self-limited headache and fever were more common among HIV-infected vaccine recipients (37%) compared with HIV-infected placebo recipients (23%) or HIV-uninfected individuals who received the vaccine (21%) (Wallace et al., 2004). Similarly, a trial among HIV-infected individuals found no significant differences in the frequency of reported signs and symptoms within 4 days of receiving either vaccine or placebo (Kemper et al., 2003).

Severe vaccine-related adverse events were uncommon (1.6% in both placebo and vaccine group with severe headache, and 1.6% of vaccine group with severe fatigue). Among patients with hemophilia, high rates of

Table 1. Selected studies on response to HAV vaccination among HIV-infected individuals.

Study author, year	Patient population	Percentage (%) who responded to vaccination*	Association of $CD4^+$ cell counts with response	Association of plasma HIV-1 viral load with response	Geometric mean titers IU/L
Crum-Cianflone et al. (2011)	130 HIV-infected individuals (military)	89	78% and 94% responded at 1 year among those with a baseline CD4<350 and ≥350 cells/mm^3 respectively, (p=0.006)	82% and 94% responded at 1 year among those with <1000 and ≥1000 copies/ml, respectively	87 and 199 at 1 year among those with <350, and ≥ 350 $CD4^+$ cells/mm^3, respectively (p=0.02). 104 and 196 among those with a baseline HIV viral load < 1000 and ≥ 1000 copies/ml, respectively
Overton et al. (2007)	268 HIV-infected individuals	50	Current $CD4^+$ cell count and $CD4^+$ nadir not associated with response rate	Those with <1000 copies/ml were 2.25 times more likely to respond than those with >1000 copies/ml	-
Kourkounti et al. (2012)	351 HIV-infected individuals with CD4 count ≥200 cells/mm^3	74 at 1 month, 68 at 6 months, 61 at 12 months, and 56 at 18 months	Responders had a higher median current $CD4^+$ cell count (580 cells/mm^3) than non-responders (528 cells/mm^3; p=0.007).	-	315 at 1 month, 203 at 6 months, 153 at 12 months, and 126 at 18 months
Tilzey et al. (1996)	Group 1: 25 HIV-infected patients with hemophilia; Group 2: 8 HIV-uninfected with hemophilia ; Group 3: 25 HIV-uninfected controls	Group 1: 76; Group 2: 100; Group 3: 100	Among Group 1, with one exception, all poor responders had $CD4^+$ counts of < 100 cells/mm^3	-	Group 1: 204; Group 2: 720; Group 3: 1354
Neilsen et al. (1997)	Group 1: 83 HIV-infected MSM; Group 2: 39 HIV-uninfected MSM	Group 1: 88; Group 2: 100	Group 1 responders had a higher mean $CD4^+$ cell count (540 cells/mm^3) than poor responders (280 cells/mm^3; p=0.03). Only 9 (64%) of Group 1 with $CD4^+$ cell counts <200 cells/mm^3 responded	-	Group 1: 107; Group 2: 1086 (p<0.001) Group 1 with $CD4^+$ cell count ≥200 cells/mm^3 130 versus 20 if $CD4^+$ cell count <200 cells/mm^3 (p=0.001)
Weissman et al. (2006)	138 HIV-infected	49	Responders had higher $CD4^+$ counts than poor responders (509 cells/mm^3 vs. 344 cells/mm^3 p = 0.001). Responders were less likely to have a $CD4^+$ count <200 cells/mm^3 (11% vs. 34% p = 0.002)	There was a trend towards having a lower log viral load among responders than non-responders (2.6 vs. 2.9, p=0.07	-
Kemper et al. (2003)	68 HIV-infected individuals as part of a RCT	52	9%, 68%, and 67% responded among those with a CD4<200, 200-499, and >500 cells/mm^3 respectively, (p=0.004)	-	23, 82, and 145 in those with <200, 200–499, and >500 $CD4^+$ cells/mm^3, respectively (p=0.02)
Wallace et al. (2004)	Group 1: 60 HIV-infected patients; Group 2: 90 HIV-uninfected as part of a RCT	Group 1: 61, 94; Group 2: 90, 100 after 1st and 2nd injections, respectively	Group 1 with a $CD4^+$ count <300 cells/mm^3, 87% responded vs. 100% with a $CD4^+$ count ≥300 cells/mm^3 at week 28	-	Group 1 with $CD4^+$<300 cells/mm^3 517; Group 1 with $CD4^+$≥ 300 1959; Group 2: 3471
Launay et al. (2008)	RCT of 99 individuals with HIV and CD4 counts between 200 to 500 cells/mm^3. Group 1: 3-dose vaccine schedule; Group 2: 2-dose vaccine schedule	Group 1: 83; Group 2: 69	Group 1 with a $CD4^+$ count between 200 and 349 cells/mm^3, 78% responded vs. 87% with a $CD4^+$ count between 350 and 500 cells/mm^3; Group 2 with a $CD4^+$ count between 200 and 349 cells/mm^3, 57% responded vs. 81% with a $CD4^+$ count between 350 and 500 cells/mm^3	-	Group 1: 324; Group 2: 138 at 28 weeks, (p=0.03)

Table 1. Contd.

Tseng et al. (2012)	Group 1: 140 HIV-infected MSM, 2-dose vaccine schedule; Group 2: 225 HIV-infected MSM, 3-dose vaccine schedule; Group 3: 217 HIV-uninfected MSM, 2-dose vaccine schedule	Group 1: 76; Group 2: 78; Group 3: 89	Among patients with HIV (Groups 1 and 2), higher CD4+ counts were associated with seroconversion (adjusted odds ratio 1.13 per 50 cells/mm^3)	Undetectable viral loads (<40 copies/ml) were associated with seroconversion (adjusted odds ratio 1.90)	Group 1: 1.74; Group 2: 2.29 at 48 weeks (p<0.01); Group 1: 1.78; Group 2: 2.08 log10 mIU/ml at 72 weeks (p<0.01)

MSM; men who have sex with men, RCT; randomized controlled trial. *These studies varied in the timing of assessment of response to vaccination and this table includes selected studies rather than all studies. It includes some of the larger studies and those that represent particular periods or include specific distinct subgroups.

adverse events after vaccination were noted, predominantly local site reactions (80%, 20 of 25 HIV-infected patients with hemophilia); however reaction rates were higher among HIV-uninfected individuals with hemophilia (96%, 24 of 25 HIV-uninfected individuals) (Tilzey et al., 1996). Another study of patients with hemophilia found no difference in the frequency of side-effects between those with and without HIV infection (Santagostino et al., 1994).

HAV vaccination impact on HIV disease severity

Safety of HAV vaccines among HIV-infected individuals is a key area of consideration given that several (Brichacek et al., 1996; Gunthard et al., 2000; O'Brien et al., 1995; Ostrowski et al., 1997; Stanley et al., 1996; Staprans et al., 1995) [but not all (Farber et al., 1996; Kroon et al., 1996)] early reports suggested HIV-1 viral load may be transiently increased by influenza and other vaccinations. An early safety study of HAV vaccine compared 90 vaccinated HIV-infected patients with 90 HIV-infected controls with similar $CD4^+$ cell counts at baseline. At 12 months, there were no significant differences in immunologic status, progression to AIDS, or death rate Between cases and controls (Bodsworth et al., 1997). A more recent study of 90 HIV-infected individuals found no significant differences between vaccine and placebo groups in $CD4^+$ counts or HIV-1 viral load levels at a number of time points after vaccination (Wallace et al., 2004). Similarly, a trial of vaccinated HIV-infected patients found no significant differences between vaccine and placebo recipients in HIV-related events including change in CDC HIV disease stage or transient increases in viral load due to vaccination (Kemper et al., 2003). These studies suggest that HAV vaccine is safe for HIV-infected individuals with no demonstrable effect on HIV-1 viral load levels, progression to AIDS, or $CD4^+$ cell counts.

CLINICAL IMPLICATIONS AND UNANSWERED QUESTIONS

Vaccination timing

Ideally, patients with HIV should be vaccinated before significant immunologic deterioration occurs. While this is not feasible for patients who present to care late in their disease course, the increased emphasis on HIV testing may lead to fewer patients with undiagnosed HIV infection. Guidelines do not make specific recommendations regarding the timing of vaccination relative to initiation of antiretroviral therapy or $CD4^+$ count, but note that response rates are poorer among those with lower $CD4^+$ cell counts (Fiore et al., 2006). Although data are lacking, a number of approaches to this problem have been described for HAV-susceptible patients including:

1. Vaccinate patients regardless of antiretroviral therapy status, check antibody levels a month or more after vaccination, and repeat vaccination for those without a vaccine response after antiretroviral therapy has been initiated, and the $CD4^+$ cell count is above 200 cells/mm^3 (Rimland et al., 2005);
2. Initiate antiretroviral therapy but delay HAV vaccination until $CD4^+$ cell counts are above > 200 cells/mm^3 (Rimland et al., 2005);
3. Initiate antiretroviral therapy and delay vaccination until HIV viral replication is controlled regardless of $CD4^+$ cell count (Overton et al., 2007).

Data regarding which strategy to pick are limited and may be further complicated in some settings by lack of availability of quantitative HAV IgG antibody testing. According to recent guidelines, data on delaying vaccination until a $CD4^+$ count is over 200 are graded as category C ("evidence for efficacy is insufficient to support a recommendation for or against") (Kaplan et al., 2009). Furthermore, delaying vaccination until immune

vaccination until immune restoration may place patients at risk of never receiving the vaccine (Tedaldi et al., 2004). In addition, the benefit of revaccination among non-responders remains unclear, graded as category B ("moderate evidence for efficacy") (Kaplan et al., 2009).

Each of these strategies focus on HAV-susceptible patients. Determining HAV-susceptibility before vaccination has implications including costs, potential vaccination delays and missed opportunities. However, given the varying prevalence rates of HAV-susceptibility in different patient groups, and the now universal childhood vaccination recommendations, screening likely remains preferable in many, if not most settings.

HAV booster vaccination or 3-dose vaccine schedules

The need for HAV booster vaccination in those without HIV remains controversial (Van Damme et al., 2003). Among HIV-uninfected individuals, initial response rates are very high, HAV antibody persistence appears to be greater than 10 years, and underlying immune memory may provide protection after the disappearance of anti-HAV antibodies (Hammitt et al., 2008; Rendi-Wagner et al., 2007; Van Damme et al., 2003; Van Herck et al., 2001). Therefore, post-vaccination testing in HIV-uninfected adults or children is not recommended (ACIP, 1996). Studies have suggested that antibodies may wane faster among HIV-infected individuals than controls (Santagostino et al., 1994; Wallace et al., 2004). One study found that 89% of HIV-infected patients responded to vaccine, among the responders, 90% still had protective HAV IgG levels ≥10 mIU/ml 3 years later, and 85% were still protected 6 to 10 years after vaccination (Crum-Cianflone et al., 2011).

Another small study found that among HIV-infected individuals who had initially responded to vaccination, 85% still had protective anti-HAV antibodies at ~4 years after vaccination, although antibody levels had decreased by ~90%, with longer duration of HIV infection and a detectable HIV viral load considered as the key predictors of loss of protection (Kerneis et al., 2011). A small trial among HIV-infected individuals with a $CD4^+$ cell count < 500 cells/mm^3 found that a 3-dose schedule seemed to induce higher seroconversion rates and higher antibody titers than the standard 2-dose schedule (Launay et al., 2008). This expanded dosing schedule added an additional dose at 1 month which may also have advantages of accelerating immunization for individuals for whom quick protection is needed, such as for travelers with unexpected trips to developing countries. More recently, a study of 2 versus 3 dose schedules found only slightly higher seroconversion rates with a 3- dose schedule but higher geometric mean titre (GMT) at 48 and 72 weeks (Tseng et al., 2012).

Further research on the rate and impact of antibody decline among HIV-infected populations is needed to inform recommendations regarding post-vaccination antibody testing, expanded dosing schedules, or booster vaccinations (Van Damme et al., 2003). However, recent European guidelines are now recommending checking anti-HAV antibody titers in high-risk patient populations such as MSM (European AIDS Clinical Society, 2011).

Clinical implications summary

Based on these studies, HAV vaccination is recommended for all HAV seronegative HIV-infected individuals (Tasker et al., 2000), or at least those with risk factors for HAV such as MSM, IDUs, as well as those with chronic liver disease (European AIDS Clinical Society, 2011; Fiore et al., 2006; Geretti et al., 2008; Kaplan et al., 2009; ACIP, 1999). Although complete data are lacking, several studies demonstrate a lower response rate to HAV vaccine among HIV-infected adults, raising the question of whether there is benefit in measuring anti-HAV antibodies after vaccination. European guidelines have recommended checking anti-HAV antibody titers in high-risk patient populations (European AIDS Clinical Society, 2011). Non-responders could then be re-vaccinated once $CD4^+$ cell counts have risen, ideally above 300 to 500 cells/mm^3 in response to HAART (Rivas et al., 2007). In addition, there may be benefit in monitoring post-vaccination HAV antibodies and providing booster vaccines to those individuals with waning antibody titers, although definitive recommendations regarding this strategy must await the results of additional studies.

Conclusions

HIV-infected individuals are often at increased risk for HAV infection, and HAV infection can cause significant morbidity and mortality among HIV-infected patients. HAV vaccination is well-tolerated and immunogenic among most HIV-infected individuals, particularly those with higher $CD4^+$ cell counts. Adverse event rates are similar among HIV-infected individuals and HIV-uninfected individuals, and HAV vaccine does not have a marked impact on HIV-1 RNA levels, progression to AIDS, or $CD4^+$ cell counts. Despite decreased immunogenicity of HAV vaccine in HIV-infected compared with uninfected individuals, seroconversion rates are still high, suggesting HAV vaccine will be effective for most HIV-infected individuals. Additional studies are needed to develop effective health promotion programs such as for hepatitis A vaccination among patients with HIV, and to determine the most effective vaccination strategies for HIV-infected patients in relation to $CD4^+$ count, HIV-1 viral load, and HAART as well as the need for re-vaccination in those with poor vaccine responses or waning antibody titers.

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UPCOMING CONFERENCES

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