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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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