A natural history of efavirenz drug-induced liver injury

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Background. Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, has been a component of first-line antiretroviral therapy (ART) in the South African HIV/AIDS programme since 2004. It is extensively used in ART programmes in other low- and middle-income countries. The natural history of the previously recognised EFV drug-induced liver injury (DILI) is not known.

Objectives. To define and establish a causality assessment for EFV DILI and document its natural history by detailing a patient cohort. All relevant features characterising the patterns of clinical and histological injury, the duration of clinical and biochemical recovery and the associated mortality rate were documented. Factors associated with specific histological patterns of liver injury were analysed.

Methods. Patients were prospectively included after meeting causality and inclusion criteria for EFV DILI. Clinical, demographic and liver histological features (where possible) were documented from the time of presentation and throughout follow-up. Prednisone at 0.25 - 0.5 mg/kg was initiated at the discretion of the treating hepatologist.

Results. Fifty patients were prospectively included in the analysis. The median age was 34 (interquartile range (IQR) 29 - 39) years, males being older than females (p=0.014). Most (92%) were female, and 86% were of black African ethnicity. The median duration of ART at presentation was 6 months, with half of the women having initiated ART during pregnancy, at a median gestation of 24 (IQR 11 - 36) weeks. The median CD4 nadir at ART treatment initiation was 517 cells/μL, with no significant difference in CD4 nadir between those who were pregnant and those who were not (p=0.6). The median RUCAM (Roussel Uclaf Causality Assessment Method) score was 7, and among the 75% of patients who had liver biopsies, three histological patterns were identified: submassive necrosis (60%), nonspecific hepatitis (35%), and mixed cholestatic hepatitis (5%). On multivariate analysis, predictors for the development of submassive necrosis included younger age (<30 years; p=0.045), ART initiation in pregnancy (p=0.02), and a baseline CD4 count >350 cells/μL (p=0.018). For the nonspecific hepatitis group, pregnancy was also an associated factor (p=0.04). The mortality rate was 14%, with a median time from admission to death of 15 days. The median (IQR) time to initial hospital discharge was a lengthy 33 (24 - 52) days. Biochemical recovery was prolonged, necessitating a follow-up period of more than a year at an outpatient specialist clinic, with 86% of patients initiating a protease inhibitor-based ART regimen successfully.

Conclusions. EFV DILI is a severe drug complication of ART with appreciable mortality and significant inpatient morbidity, requiring prolonged hospitalisation and follow-up.

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Sub-Saharan Africa carries the greatest global HIV/AIDS burden. South Africa (SA), an epicentre for HIV/AIDS, has an estimated adult HIV prevalence of ~12.6%.[1] In 2016, an estimated 7.1 million South Africans were living with HIV, of whom 56% were accessing antiretroviral therapy (ART).[2] More than 95% of HIV-positive pregnant women were accessing treatment to prevent mother-to-child transmission of HIV.[2]

Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), has formed part of the SA national first-line ART since 2004. Subsequently, with the introduction of a fixed-dose combination (FDC) formulation with tenofovir and emtricitabine, EFV became the favoured first-line NNRTI in 2015. A change in SA government policy necessitated the treatment programme change.[3] Importantly, HIV-positive pregnant women were prioritised for immediate ART initiation with EFV-based first-line therapy when the World Health Organization deemed it safe for use in pregnancy after initial concerns.[4] As a result, all HIV-positive pregnant or breastfeeding women are currently commenced on lifelong ART with EFV as part of the first-line regimen in many programmes, regardless of CD4 count or duration of gestation, especially in low- and middle-income countries (LMICs).[5]

Documented adverse effects of EFV include most notably the neuropsychiatric effects of insomnia, depression and EFV encephalopathy.[6] These side-effects are thought to be dose-related and can be attributed to the 'slow-metaboliser' phenotypes where cytochrome P450 2B6 (CYP2B6) genotypic polymorphism combinations result in elevated plasma EFV concentrations in HIV-infected black African adults and children.[7] There are no data to suggest that similar mechanisms are linked to its hepatotoxic potential.

Alhough hepatotoxicity is well described in the NNRTI class of antiretrovirals, it is nevirapine (NVP) as opposed to EFV that has the higher reported incidence of drug-induced liver injury (DILI). This well-described hypersensitivity reaction is marked by rash, eosinophilia and hepatitis (a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome phenomenon) and typically

occurs early (within the first 2 months of taking NVP), is observed more commonly in women, and is associated with higher body mass index (BMI).[8]

Drug hepatotoxicity with EFV is recognised, but is reported to occur at a frequency far less than with NVP. No particular characteristics have been associated with EFV hepatotoxicity, and the natural history of EFV DILI is as yet not described. In SA, three distinct clinicopathological patterns of EFV DILI were defined in 2016.[9] One histological pattern, submassive necrosis, was associated with significant morbidity and mortality. The biochemical, clinical and histological features of this novel injury indicated that it was a severe injury requiring prolonged hospitalisation, and predictors of risk included female gender, higher CD4 nadir at drug initiation, and younger age.[9]

There is very little information on EFV DILI in the literature. A few case reports describe strong causality with regard to suspected EFV DILI, with little documented on the natural history and clinical manifestations of the injury.[10-13]

Objectives

We prospectively documented patients with EFV DILI to evaluate and describe the natural history of this novel injury, including clinical and histological characteristics, management and outcomes.

Methods

We conducted an observational, prospective cohort study of patients presenting to the Division of Hepatology/Liver Clinic at Groote Schuur Hospital, Cape Town, SA, and identified as meeting causality criteria for EFV DILI.

Inclusion criteria for EFV DILI were: (*i*) a temporal relationship between drug exposure and clinical disease; (*ii*) exclusion of acute viral hepatitis (hepatitis A, B, C and E); (*iii*) antinuclear factor and/or anti-smooth-muscle antibody ≤1:80 plus histological features not compatible with autoimmune hepatitis; (*iv*) radiological exclusion of biliary and vascular obstruction; (*v*) exclusion of alcohol/herbal toxins; and (*vi*) observing the effects of drug dechallenge and a histological injury pattern (if biopsy feasible) compatible with a DILI. For viral hepatitis specifically, hepatitis E was assessed by means of an in-house hepatitis E polymerase chain reaction (PCR) test rather than serology, given the low sensitivity and specificity of available commercial kits in our service.[14] Hepatitis A IgM, hepatitis B surface antigen and core IgM and hepatitis C antibody (Abbot ARCHITECT, USA) were screened to exclude acute hepatitis A, B and C. Additionally, the RUCAM (Roussel Uclaf Causality Assessment Method) causality model was used as a causality assessment tool to categorise the likelihood of EFV being causative.[15] The RUCAM scale involves a scoring system that categorises the suspicion of a DILI into 'definite or highly probable' (score >8), 'probable' (score 6 - 8), 'possible' (score 3 - 5), 'unlikely' (score 1 - 2) and 'excluded' (score 0).

Prospectively, patients fulfilling causality for EFV DILI had relevant clinical and demographic data collected following informed and written consent. At the discretion of the treating hepatologist, and with sepsis excluded, patients were initiated on oral prednisone at 0.25 - 0.5 mg/kg, starting at a low dose and titrating according to response. Once biochemical normality or the patient's baseline was achieved, progressive weaning of steroids occurred until complete discontinuation, at which time patients were discharged back to primary care.

The patients' clinical course and biochemical recovery were documented up to at least 12 months after initial presentation. Follow-up after hospital discharge took place at the Liver Clinic, Groote Schuur Hospital. Recovery was defined as a return of the liver profile to normal or to the patient's baseline before ART initiation, if known, in addition to complete resolution of initial clinical symptoms. The cumulative dose of immunosuppressive therapy was extracted from the electronic Medicines Management System.

As part of the standard of care in assessing causality and requirement for corticosteroid therapy (presence of immune-allergic pattern of injury with inflammation), liver biopsies (including trans-jugular biopsies, if clinically warranted) were performed unless uncorrectable coagulopathy or clinical risk precluded a safe procedure.

Histological patterns of EFV DILI are immune-allergic in nature, and in standardising EFV DILI histological patterns of injury reporting, the following three patterns were noted:[9]

Submassive necrosis. Morphologically zonal or panzonal necrosis with inflammatory cell infiltrates composed of lymphocytes, plasma cells, and conspicuous eosinophils.

Nonspecific hepatitis with portal and/or lobular inflammation particularly in zone 3 with/without cholate stasis in zone 1, with inflammatory cells including lymphocytes and eosinophils.

Mixed cholestatic hepatitis. A combination of portal tract inflammation/interface hepatitis with inflammatory cells, including lymphocytes and eosinophils with marked zone 3 bilirubinostasis and a ductular reaction.

Eosinophils were anticipated in all three histological patterns of injury as part of the inflammatory cell infiltrate.[9]

Ethics approval was obtained from the Faculty of Health Sciences Human Research Ethics Committee at the University of Cape Town (ref. no. 593/2018).

Statistical analysis

Statistical analyses were performed using Stata release 15, 2017 (StataCorp. USA). Demographic and clinical characteristics were summarised with descriptive statistics. Categorical variables were presented as frequencies and percentages. Means and standard deviations were used for normal or parametric distributed data and medians with interquartile ranges (IQRs) for non-parametric data. Continuous variables were compared using either Student's *t*-test (parametric) or the Wilcoxon rank-sum test (non-parametric). For laboratory data that included more than two groups, the Kruskal-Wallis and Mann-Whitney *U*-test/Wilcoxon rank-sum test were utilised for non-parametric data. Logistic regression multivariate analysis was performed on factors found significant on univariate analysis to identify potential factors associated with the two dominant histological patterns of liver injury (the third pattern was too few in numbers to analyse meaningfully). All regression estimates were presented with 95% confidence intervals, and all *p*-values were considered significant at $p<0.05$.

Results

Fifty patients met the causality criteria for EFV DILI and were prospectively included in the analysis. An additional 7 patients were evaluated but were not included. Of these 7 patients, 2 died shortly after admission and were unable to provide consent, 2 had probable isoniazid (INH) DILI, 2 were diagnosed with autoimmune hepatitis, and 1, who was on EFV and then switched to NVP, probably had NVP DILI. The baseline demographic characteristics of the patients are listed in Table 1. Notably, most patients (n=46; 92%) were female and most were of black African ethnicity (n=43; 86%). The median (IQR) age was 34 (29 - 39) years, males being older than females (p=0.014) (although there were very few men, n=4). The median (IQR) BMI was 25 (22 - 23), with a range from normal to obese BMI.

Table 1. Baseline demographic data (*N*=50 patients)

Parameters		*p*-value*
Age (years), median (IQR)	34 (29 - 39)	
Females	34 (29 - 38)	
Males	43 (39 - 49)	0.014
Gender, *n* (%)		
Female	46 (92)	
Ethnicity, *n* (%)		
Black African	43 (86)	
Mixed ancestry	7 (14)	
BMI (kg/m^2), median (IQR)	25 (22 - 33)	
ART initiated in pregnancy, *n* (%)	23 (46)	
Months post partum at presentation, median (IQR)	3 (2 - 6)	
CD4 count† (cells/μL), median (IQR)	517 (348 - 722)	
Pregnant (*n*=23)	553 (424 - 792)	
Not pregnant (*n*=27)‡	424 (301 - 658)	0.6
Female	539 (354 - 780)	0.07
Male	152 (109 - 289)	
Duration of ART (months), median (IQR)	6 (5 - 10)	
Alcohol consumption,§ *n* (%)	14 (28)	
HBsAg-positive, *n* (%)	2 (4)	
HBV core IgM-positive, *n*/*N*	0/2	
HBV viral load <20 IU/mL, *n*/*N*	2/2	
HCV antibody-positive, *n* (%)	0	
HEV IgM antibody-positive, *n* (%)	1 (2)	
HEV PCR-positive, *n*/*N*	0/1	
Autoimmune serology, *n* (%)		
Antinuclear antibody-positive	1 (2)	
Anti-smooth-muscle antibody-positive	8 (16)	
Titre ≤1:100	8 (16)	
Anti-liver kidney microsomal type 1 antibody-positive	0	
Medication use, *n* (%)		
Co-trimoxazole	1 (2)	
INH prophylaxis	6 (12)	
Anti-TB drugs (INH/RIF/PZA/EMB)	3 (6)	
Fluconazole	0	
Herbal/traditional	3 (6)	
Other	1 (2)	

IQR = interquartile range; BMI = body mass index; ART = antiretroviral therapy; HBsAg = hepatitis B surface antigen; HBV = hepatitis B; HCV = hepatitis C; HEV = hepatitis E; PCR = polymerase chain reaction; INH = isoniazid; TB = tuberculosis; RIF = rifampicin; PZA = pyrazinamide; EMB = ethambutol.
**p*-values for univariate analysis.
†CD4 nadir.
‡Included 4 males.
§Defined as consuming any alcohol >1 unit per week.

The median (IQR) duration of ART at the time of presentation was 6 (5 - 10) months. Half of the women had initiated ART during pregnancy, at a median (IQR) gestation of 24 (11 - 36) weeks. Where ART was initiated in pregnancy, patients presented a median (IQR) of 3 (2 - 6) months after delivery. Notably, the median CD4 nadir at ART treatment initiation was 517 cells/μL, with no significant difference (p=0.6) in CD4 nadir between patients who were pregnant and those who were not.

With regard to reported alcohol use, 28% drank alcohol, although typically this did not exceed 4 units of alcohol per week. Autoimmune serology was positive in 9 patients, with 1 patient antinuclear antibody- and 8 anti-smooth-muscle antibody-positive. The auto-antibody titres were all low at ≤1:100. Significantly, liver biopsies were not compatible with an autoimmune hepatitis pattern of injury in these patients. Two patients were co-infected with hepatitis B, both hepatitis B e-antigen-negative with an undetectable hepatitis B DNA viral load at presentation. Hepatitis C antibody was not detected in any patient. No patients were hepatitis E virus PCR-positive.

Table 2 notes the median (IQR) RUCAM score of 7 (6 - 9), denoting EFV DILI in the probable category. Of the 50 patients, 6 (12%) had received INH preventive therapy and 3 previous tuberculosis (TB) therapy, while 1 patient had previously been on co-trimoxazole prophylaxis. The clinical course, histological findings and temporal relationship with drug use and clinical onset were not compatible with INH- or co-trimoxazole-induced liver injuries. Given the severity of the injury, EFV rechallenge was not attempted in any of the patients. The RUCAM score therefore did not reflect the three potential additional points from a failed EFV rechallenge.

The median (IQR) duration of admission or time to initial discharge from hospital was 33 (24 - 52) days. The median (IQR) time

Table 2. Clinical and follow-up characteristics (*N*=50 patients)

RUCAM score, median (IQR)	7 (6 - 9)
Clinical features, *n* (%)	
Jaundice	47 (94)
Skin rash	0
EFV encephalopathy*	2 (4)
Outcome	
Recovery, *n* (%)	37 (74)
Duration of admission (days), median (IQR)	33 (24 - 52)
Duration of outpatient follow-up, median (IQR)	574 (239 - 728)
Death, *n* (%)	7 (14)
Time to death (days), median (IQR)	15 (10 - 16)
Lost to follow-up, *n* (%)	6 (12)
Cumulative dose of prednisone (mg), median (IQR)	3 198 (1 898 - 4 670)
Duration of treatment with steroids (prednisone) (months), median (IQR)	11 (8 - 16)
Complications, *n* (%)	
Sepsis (culture-positive)	3 (6)
Sepsis (culture-negative)	7 (14)
Steroid-induced DM	5 (10)
Current ARV regimen, *n*	
FTC/TDF/RTV/ATV	16
FTC/TDF/LPV/RTV	20
3TC/ABC/LPV/RTV	1
Unknown (lost to follow-up)	6

RUCAM = Roussel Uclaf Causality Assessment Method; EFV = efavirenz; DM = diabetes mellitus; ARV = antiretroviral; FTC = emtricitabine; TDF = tenofovir; RTV = ritonavir; ATV = atazanavir; LPV = lopinavir; 3TC = lamivudine; ABS = abacavir.
*EFV levels within toxic range (both patients >20 mg/L with therapeutic range 1 - 4 mg/L).

to biochemical recovery was 574 (239 - 728) days. Fig. 1 graphically notes the trends in median liver profile parameters over the initial 12-month period following presentation. Jaundice resolved between months 3 and 6, with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) time to normalisation extending well beyond 6 months.

Among the 74% of patients who had liver biopsies (*n*=37), three histological patterns were identified: submassive necrosis (*n*=22; 60%), nonspecific hepatitis (*n*=13; 35%) and mixed cholestatic hepatitis (*n*=2; 5%). All three of these patterns were associated with grade 4 ALT elevation (using the modified AIDS Clinical Trial Group grading).[16]

Despite the immune-allergic nature of the liver histological pattern, no patients had any skin rash associated with EFV DILI.

The most severe injury, clinically, biochemically and histologically, was submassive necrosis. Table 3 sets out these patterns of liver profiles at presentation. Bilirubin was significantly more elevated with this pattern of injury compared with the nonspecific hepatitis or mixed cholestatic hepatitis patterns (p=0.012). This occurred in the absence of a significant difference in ALT presentation in the three patterns (713, 927 and 510 U/L, respectively; p=0.55). Synthetic dysfunction at presentation, as measured by the international normalised ratio, was significantly greater in the submassive necrosis group compared with the other two pattern of injury groups (1.72, 1.19 and 1.13, respectively; p<0.0001).

On univariate analysis, the following parameters were significantly associated with the two dominant histological patterns, submassive necrosis and nonspecific hepatitis: age <30 years (p=0.008 and p=0.080, respectively); CD4 nadir >350 cells/μL (p=0.001 and p=0.05, respectively); pregnant when ART initiated (p=0.001 and p=0.06, respectively); alcohol use (p=0.1 and p=0.015, respectively), and BMI >25 kg/m^2 (p=0.02 and p=0.1, respectively). Table 4 reflects the multivariate logistic regression analysis of significant parameters on univariate analysis. Factors significantly associated with the development of submassive necrosis included younger age (<30 years; p=0.045), ART initiation in pregnancy (p=0.02), and a baseline CD4 count >350 cells/μL (p=0.02). For the nonspecific hepatitis group, only pregnancy was an associated factor (p=0.03).

Most patients (*n*=42; 84%) were treated with corticosteroids. The median (IQR) duration of treatment with prednisone was 11 (8 - 16) months, with a cumulative prednisone dose of 3 198 (1 898 - 4 670) mg. All patients were successfully weaned from corticosteroids. Ten patients had episodes of in-hospital sepsis, of whom 3 were culture-positive and 7 were culture-negative when a presumptive diagnosis based on clinical criteria was made. Steroid-induced diabetes mellitus occurred in 10% (*n*=5). During follow-up, 86% (*n*=37/43) were restarted successfully on protease inhibitor (PI)-based ART and 70% (*n*=30/43) were virologically suppressed at their last visit. No patients met clinical criteria for TB immune reconstitution inflammatory syndrome.

The mortality rate was 14% (*n*=7), all deaths occurring within the first 16 days after presentation. All deaths occurred in the patients who were not biopsied, as poor general clinical condition and coagulopathy precluded a safe procedure.

Discussion

We report the first study documenting the natural history of EFV DILI. Several insights have emerged that allow for better clinical understanding and therefore better patient management. A long latency period of 6 months from initiation of the EFV-based ART to presentation complicates the development of clear guidance for patients at risk, given that regular monitoring for the large number of patients in the national ART programme will be logistically challenging. Furthermore, unlike NVP DILI, there are no phenotypic features of a hypersensitivity or DRESS-type syndrome observed with the liver injury. This lack compounds the difficulty in detection

Table 3. Laboratory parameters* of the three histological patterns of efavirenz-related drug-induced liver injury (*N*=33 liver biopsies performed)

	Pattern of injury			
Laboratory parameters	Submassive necrosis (*n*=19), median (IQR)	Nonspecific hepatitis (*n*=12), median (IQR)	Mixed cholestatic hepatitis (*n*=2), median	*p*-value
Total bilirubin (µmol/L)	272 (210 - 317)	93 (63 - 276)	87	0.012
Conjugated bilirubin (µmol/L)	165 (117 - 228)	67 (16 - 156)	48	0.0054
ALT (U/L)	713 (470 - 1 445)	927 (389 - 1 174)	510	0.55
AST (U/L)	1 055 (571 - 1 966)	876 (374 - 1 403)	729	0.19
ALP (U/L)	296 (173 - 389)	170 (131 - 203)	271	0.0082
GGT (U/L)	229 (143 - 596)	264 (142 - 538)	615	0.7
INR	1.72 (1.5 - 2.28)	1.19 (1.1 - 1.4)	1.13	<0.0001
CD4 (cells/µL)†	553 (415 - 743)	538 (258 - 665)	205	0.033

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; INR = international normalised ratio.
*Laboratory parameter (laboratory reference range). Data are expressed as medians and interquartile ranges.
†Nadir CD4 count at the initiation of antiretroviral therapy.

Table 4. Multivariate logistic regression analysis of factors associated with histological patterns of efavirenz drug-induced liver injury

Factor	Submassive necrosis, OR (95% CI); *p*-value	Nonspecific hepatitis, OR (95% CI); *p*-value
Age <30 years*	1.5 (1.3 - 8.4); 0.045	1.04 (0.6 - 4.9); 0.7
Pregnancy†	7.1 (1.4 - 36.1); 0.018	0.2 (0.4 - 0.9); 0.03
CD4 >350 cells/µL‡	5.4 (1.1 - 26.2); 0.02	4.4 (0.8 - 2.7); 0.2
Alcohol use	1.1 (0.8 - 1.2); 0.08	3.1 (0.8 - 12.9); 0.12
BMI§	2.3 (0.6 - 9.9); 0.25	0.7 (0.2 - 2.7); 0.5

OR = odds ratio; CI = confidence interval; BMI = body mass index.
*Age at ART initiation.
†Pregnant when ART initiated.
‡CD4 nadir prior to ART initiation.
§Calculated at presentation.

of this drug injury. Jaundice is a universal presenting feature, and its presence should prompt clinicians to terminate therapy immediately and investigate for a possible DILI.

From an epidemiological perspective, our cohort probably represents typical HIV epidemiology in SA. Although we had few males, our female patients were significantly younger than the males, and the CD4 count at ART initiation in men was significantly lower than that in women. Both these demographic features are in keeping with known HIV/AIDS epidemiology in SA.[17] At lower CD4 counts, males tended to develop the mixed cholestatic-hepatitis pattern of injury. This is understandable, given our finding that a high baseline CD4 count is a clear risk factor for the submassive necrosis pattern of injury. Previous data inferred several predictors for this pattern of injury, including female gender, CD4 count and younger age.[9] Our study strengthened the findings of younger age and higher baseline CD4 count as associations with the more severe submassive necrosis injury pattern. The predominance of female gender in our prospective cohort is intriguing. Female gender has long been suggested as a risk factor for DILI.[18] However, this association was questioned in a study from Iceland, where female gender was not shown to be a risk factor for the development of DILI.[19] An association with initiation of the drug in pregnancy was demonstrated in our study, with almost half of our patients having started ART in pregnancy. These two parameters – gender and pregnancy – are compelling, but we are unable to establish for bias, given that HIV screening and treatment initiation is universal in our antenatal care programme. Pregnant women are therefore routinely screened and immediately linked to ART if HIV-positive, irrespective of CD4 count, as per policy.[5] Further data are required to understand the significance of the association of EFV DILI and pregnancy, as it may have important programmatic implications for antiretroviral programmes using EFV as first-line therapy in populations at risk. This may be a factor to be considered in recommending DILI surveillance in pregnant and postpartum women initiated on EFV in pregnancy, and in deciding whether EFV should be used as part of an ART regimen when initiated in pregnancy.

The morbidity and mortality associated with EFV DILI are substantial, characterised by the need for prolonged hospital admission (median 38 days) and a long follow-up period of more than a year. The mortality rate of 14% is significant and is in keeping with 'Hy's law', denoting that jaundice and hepatocellular injury from a drug results in a mortality rate of at least 10%.[20] Death occurred within the first 2 weeks of admission in all patients who died, with most of these deaths occurring early. These patients had a severe coagulopathy that precluded safe biopsy, but were very likely to have had submassive necrosis as their pattern of injury.

Given the conspicuous mixed inflammatory cell immune-allergic pattern of injury on liver biopsy, initiation of 0.25 - 0.5 mg/kg of prednisone was standard of care, unless a contraindication precluded its immediate use. Weaning of corticosteroids with monitoring of liver enzymes commenced after 3 - 6 months and in most patients was completed at 12 months, after initiation of new PI-based ART. The use of corticosteroids in drug injuries is not standard of care, although they are often used, and data on their use are limited. There is a need for controlled trial data.[21]

Notably, positive autoimmune serology was present, albeit at low titres, in 9 patients. However, the clinicopathological correlation for autoimmune hepatitis was weak. Firstly, anti-smooth-muscle antibodies can be nonspecifically detectable in the setting of significant liver necrosis, as in submassive necrosis.[22] Secondly, the histological

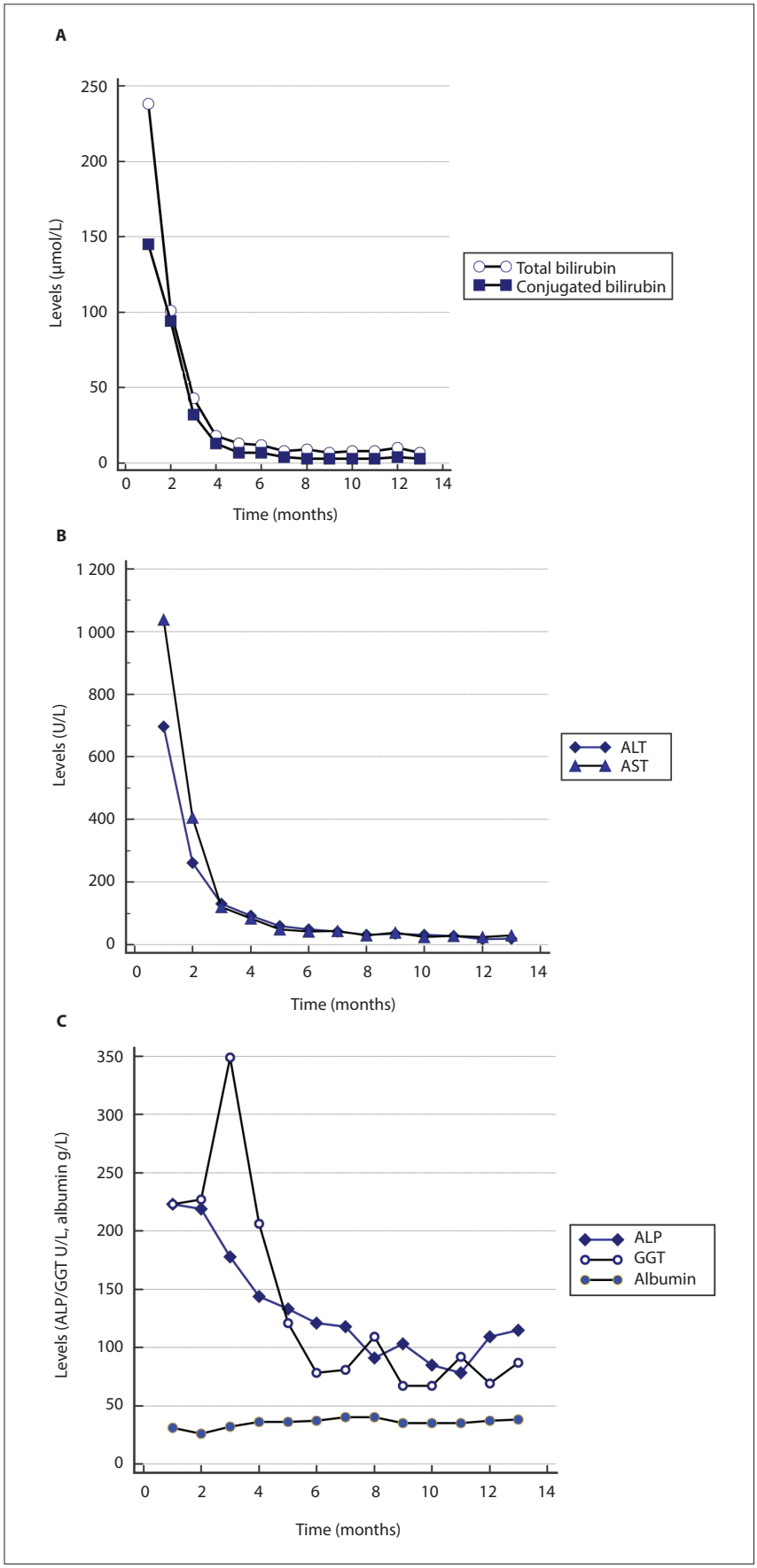

Fig. 1. Trends in liver profile parameters over 1 year of follow-up: (A) total and conjugated bilirubin; (B) ALT and AST; and (C) ALP, GGT and albumin. (ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase.)

findings were highly compatible with DILI and not autoimmune hepatitis, including an inflammatory cell infiltrate composed of mostly lymphocytes and eosinophils and scanty plasma cells. Lastly, the patients were all successfully weaned off steroid therapy in a relatively short space of time, an unlikely occurrence in autoimmune hepatitis. Biochemical stability was maintained off immunosuppression, and the majority of patients were successfully rechallenged on a PI-based regimen.

Further understanding of this liver injury, particularly the mechanisms at play in its aetiology, is crucial to identifying patients at risk. These mechanisms are likely to be multifactorial, including genetic, possibly related to CYP2B6 polymorphisms, as well as immunological, given the higher CD4 counts in patients with the most aggressive histological and clinical patterns of injury.[23] What these factors are, almost certainly related to both HLA and non-HLA haplotype polymorphisms or variants, warrants further study. Also, with the number of patients accessing ART in a population with a possible predisposition to the 'slow-metaboliser' phenotype of CYP2B6 polymorphisms, genetic studies will potentially identify those patients at risk for EFV DILI in sub-Saharan Africa.[7] We are continuing further work in this respect.

Identification of this novel liver injury in 2016 did not lead to any significant programmatic changes in SA's national ART guidelines. However, increased awareness of the injury was important in order to identify patients earlier and stop EFV appropriately. To this end, the Department of Health acted to educate clinicians about the novel aspects of EFV DILI and the importance of improved pharmacovigilance. Likewise, the drug regulator, the South African Health Products Regulatory Authority (SAHPRA), amended package inserts for EFV-containing ART. The hepatoxicity of EFV was not initially appreciated at the time of initial registration of the drug in the late 1990s. This failure to recognise hepatotoxicity as an issue with EFV emphasises the need for continued pharmacovigilance post drug marketing, especially in population groups not included in the initial drug trials. This phenomenon is not unique to EFV, but is of relevance to therapies seldom trialled in LMICs during initial registration studies.

In ART-naive patients, the recommended regimen in SA is now the tenofovir/lamivudine/dolutegravir FDC. Although the absolute risk of neural tube defects is <0.05%, it is recommended that the risks and benefits of dolutegravir-based v. EFV-based ART should be discussed with women

of reproductive age or pregnant women.[24,25] EFV-based ART will therefore foreseeably still be prescribed in women of reproductive age or pregnant women, with the potential risks of severe EFV-induced liver injuries.[26]

Study limitations

The cohort size was relatively small and could be considered a study limitation; however, for a DILI, the numbers are significant. It was a single-centre study, although we are a regional and supra-regional referral centre. Even so, selection and referral bias is a consideration. The study was not significantly powered to be able to identify any significant predictors for death or prolonged time to recovery. However, given the fact that the natural history of EFV DILI has never been described, it provides important insight into the severity of the liver injury, in terms of both morbidity and mortality. We also did not calculate or infer an incidence of this DILI, given that although the number of people on ART in our referral region is known (in 2020, 206 591 people were on ART in the City of Cape Town metropolitan area – personal communication, Western Cape Province HIV Directorate), we lack precise data on numbers of people on EFV-based ART. Additionally, the significant movement of patients between provinces limits any potential estimation in this respect.

Conclusions

EFV DILI is a novel and severe injury associated with significant morbidity and mortality. Hospital admission and outpatient follow-up are prolonged, with a need for adjunctive steroid therapy. CD4 counts >350 cells/μL, younger age and ART initiated in pregnancy were predictive for development of the severe submassive necrosis histological pattern of injury. EFV is likely still to be used, particularly in women of reproductive age, despite the introduction of dolutegravir as first-line therapy in the national ART programme since 2020. Furthermore, EFV is likely to remain in use in other LMICs for the foreseeable future. It is therefore vitally important to further elucidate the mechanisms underlying the injury, as well as improve pharmacovigilance, particularly in pregnant women on ART.

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