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ADVERSE DRUG REACTIONS WITH COMMON ANTIVIRALS IN VIRAL HEPATITIS: A *PROSPECTIVE OBSERVATIONAL STUDY FROM A NORTH-INDIAN TERTIARY-CARE OPD*

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ABSTRACT

Background: Antiviral therapy is central to viral hepatitis care, yet real-world adverse drug reaction (ADR) patterns in busy outpatient settings remain incompletely characterised.

Aim: To evaluate ADRs associated with antivirals used for viral hepatitis, focusing on frequency, severity, time-to-onset, and causality.

Materials and Methods: A prospective, observational study conducted in the Gastroenterology and Medicine outpatient departments of KGMU, Lucknow after ethics approval (IEC 3006/Ethics/2024, 23-01-2024). Adults with viral hepatitis receiving antivirals were enrolled (n = 95) after consent. ADRs were captured using a pre-designed case-record form and assessed by WHO-UMC causality and Hartwig severity scales; follow-up was scheduled at ~1 month and thereafter per protocol, with review after any ADR. Statistical analyses included paired t-tests, chi-square tests, and Kruskal–Wallis (two-sided $p < 0.05$).

Results: Antivirals prescribed were tenofovir, entecavir, sofosbuvir+daclatasvir and sofosbuvir+velpatasvir. From baseline to follow-up, there were significant improvement in biochemical parameters, decrease in AST/SGOT, ALT/SGPT, ALP, urea, creatinine, and INR, and increase in serum protein and albumin. ADRs occurred in 31/95 (32.6%); Most frequent ADRs were nausea, headache, and fatigue. Most ADRs were mild. Causality was probable/possible in all cases.

Conclusion: In tertiary-care practice, antiviral therapy for viral hepatitis was associated with favourable biochemical trajectories & mild ADRs. ADR type & onset timing differ, supporting early monitoring & standardised documentation to optimise safety.

Keywords: Viral hepatitis; Antiviral agents; Adverse drug reactions; Pharmacovigilance; Tenofovir; Entecavir; Sofosbuvir.

Introduction

Viral hepatitis remains a major driver of global liver-related mortality. Recent estimates indicate ~1.3 million deaths in 2022, with hepatitis B and C accounting for the vast majority, underlining the need for effective treatment coupled with vigilant safety monitoring[1].

Current pharmacotherapy relies primarily on oral nucleos(t)ide analogues for chronic hepatitis B and direct-acting antivirals for hepatitis C. While these agents are highly effective and generally well tolerated, clinically relevant adverse drug reactions (ADRs) do occur. For hepatitis B treatments, long-term nucleos(t)ide analogue therapy, particularly with tenofovir disoproxil fumarate has been associated with renal dysfunction and bone effects, prompting consideration of agent selection and ongoing laboratory monitoring[3, 4, 5].

For hepatitis C, all-oral direct-acting antiviral regimens achieve high cure rates and have a favourable safety profile; nevertheless, real-world pharmacovigilance continues to document mostly mild but sometimes clinically significant ADRs, reinforcing the need for structured monitoring during therapy[6, 7, 8].

Despite progress under the Pharmacovigilance Programme of India, under-reporting remains a persistent challenge, highlighting the value of systematic, prospective documentation of ADRs using standardized tools[9, 10, 11].

Against this backdrop, we undertook a prospective observational evaluation of ADRs among patients receiving antiviral therapy for viral hepatitis in a tertiary-care outpatient setting in North India[12].

Materials and Methods

Study setting

This was a prospective, observational study conducted by the Department of Pharmacology & Therapeutics in collaboration with the Departments of Gastroenterology and Medicine at King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India. The study was carried out over one year.

Ethics The study received approval from the Institutional Ethics Committee, KGMU (IEC approval no. 3006/Ethics/2024, dated 23-01-2024). Written informed consent was obtained from all participants; confidentiality and anonymity were maintained.

Study population and sample size

Adults with a diagnosis of viral hepatitis receiving antiviral therapy were enrolled. The minimum sample size was 95, expected ADR prevalence p = 0.162, and margin of error 0.075.

Eligibility criteria

Inclusion: age ≥18 years; either sex; diagnosed viral hepatitis; receiving antiviral drugs; pregnant or lactating women on antiviral therapy who developed an ADR; provided informed consent. Exclusion: age <18 years; incomplete/inadequate records; refusal of consent; pre-existing comorbid conditions likely to confound ADR assessment.

Data collection and follow-up

Consecutive eligible patients were enrolled. Baseline demographics, medical and drug history, examination findings, and routine laboratory investigations (haematology, liver and renal function tests, electrolytes, coagulation profile, viral markers, thyroid profile) were recorded in a pre-designed

Case Record Form. Follow-up was scheduled at 1 month after initiation of antiviral therapy and thereafter at regular intervals.

Patients with ADRs were monitored every third day for the first two weeks, then every 30 days for at least three months post-reaction to document resolution or persistence.

Outcomes and operational definitions

The study evaluated: (i) frequency of ADRs by antiviral drug, (ii) severity of ADRs, (iii) time-to-onset of ADRs (days from therapy initiation to first reaction), and (iv) causality category for each ADR.

Time-to-onset was defined as days from the start of antiviral therapy to the first ADR; descriptive parameters (mean ± SD, range) were recorded.

ADR assessment

Causality was assessed using the WHO-UMC criteria; severity was graded using Hartwig's Severity Assessment Scale.

Statistical analysis

Data were compiled in Microsoft Excel(office 2021) and analysed using R software. Categorical variables were summarized as frequencies/percentages and compared using Chi-square tests. Continuous variables were summarized as mean ± SD; t-tests were applied where appropriate. A two-sided $p < 0.05$ denoted statistical significance. Where distributional assumptions were not met, non-parametric tests (e.g., Kruskal–Wallis) were used.

Results

Two hundred fifty patients were screened, out of whom 95 patients were included (mean age 43.47 ± 13.44 years; range 22–82. Males comprised 62.1% (59/95) and females 37.9% (36/95). The most frequently prescribed antiviral was tenofovir (38.1%, 37/95), followed by entecavir (28.9%, 28/95), sofosbuvir + daclatasvir (17.5%, 17/95) and sofosbuvir + velpatasvir (15.5%, 12/95). There was significant improvement in biochemical parameters as shown in Table1

Table 1: Biochemical parameters

Parameter	Baseline (mean ± SD) day= 0	Follow-up (mean ± SD) day= 90	P- value*
SGOT (U/L)	95.55 ± 128.15	85.46 ± 113.91	<0.05
SGPT (U/L)	98.26 ± 126.24	88.34 ± 113.52	<0.05
S. Alkaline phosphatase (U/L)	264.01 ± 127.13	236.58 ± 113.64	<0.05
S. Protein (g/dL)	7.04 ± 1.14	7.39 ± 1.20	<0.05
S. Albumin (g/dL)	4.03 ± 1.31	4.23 ± 1.37	<0.05
S. Urea (mg/dL)	35.59 ± 37.25	31.97 ± 33.04	<0.05
S. Creatinine (mg/dL)	1.07 ± 0.98	0.97 ± 0.89	<0.05
Prothrombin time (INR)	3.43 ± 7.48	3.13 ± 7.03	<0.05

(SGOT- Serum Glutamic Oxaloacetic Transaminase; SGPT- Serum Glutamic Pyruvic Transaminase)

* Paired t test was applied for comparison

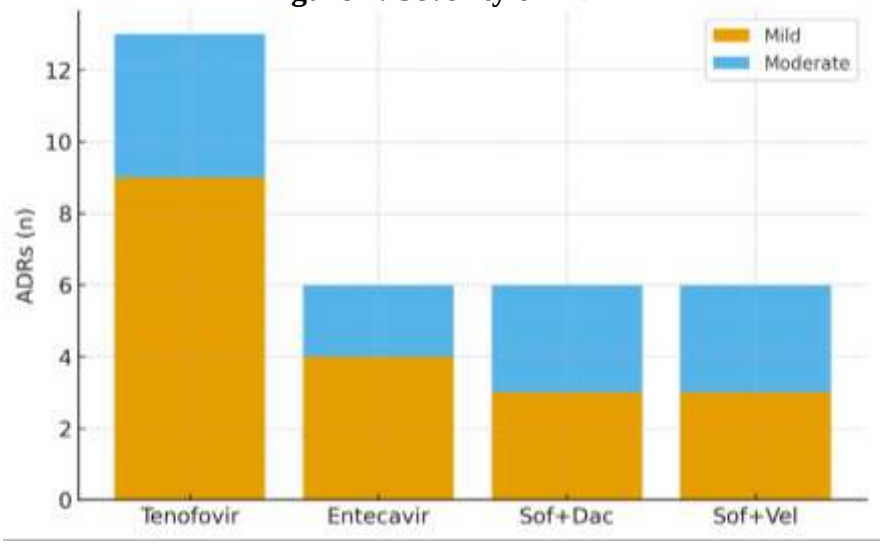
The most frequent ADRs were nausea (10.5%), headache (8.4%) and fatigue (8.4%); insomnia (2.1%), diarrhoea (2.1%) and dizziness (1.1%) were less common. Table2. The type of ADR differed significantly by antiviral ($\chi^2 = 33.53$, df = 15, $p = 0.0039$)

Table 2: ADR type, frequency & mean onset(days)

Drug	ADRs, n (%)	Common ADRs (n)	Mean Onset ± SD (days)
Tenofovir (n=37)	13 (41.94)	Nausea (8), Fatigue (2), Headache (1), Diarrhoea (2)	4.77 ± 4.85
Entecavir (n=28)	6 (19.35)	Headache (4), Dizziness (1), Nausea (1)	6.83 ± 2.32
Sofosbuvir + Daclatasvir (n=17)	6 (19.35)	Fatigue (2), Insomnia (2), Headache (1), Nausea (1)	9.83 ± 3.97
Sofosbuvir + Velpatasvir (n=12)	6 (19.35)	Fatigue (4), Headache (2)	12.83 ± 3.43

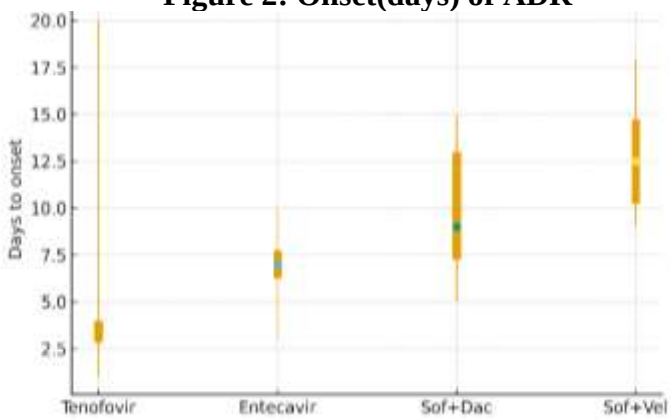
By Hartwig grading, ADRs were predominantly mild across agents. Figure1. Severity distribution did not differ by drug ($\chi^2 = 1.06$, df = 3, p = 0.786).

Figure 1: Severity of ADR



Median (IQR) onset times (days) were 3.0 (3.0–4.0) for tenofovir, 7.0 (6.25–7.75) for entecavir, 9.0 (7.25–13.0) for sofosbuvir + daclatasvir and 12.5 (10.25–14.75) for sofosbuvir + velpatasvir; differences across drugs were significant (Kruskal–Wallis H = 15.78, p = 0.0013) (Table 2, Figure 2). On WHO-UMC assessment, tenofovir ADRs were probable (n = 8) and possible (n = 5); for entecavir, sofosbuvir + daclatasvir and sofosbuvir + velpatasvir, each had probable (n = 4) and possible (n = 2)

Figure 2: Onset(days) of ADR



Discussion

This prospective, outpatient study systematically characterised adverse drug reactions (ADRs) associated with commonly used antivirals for viral hepatitis. In chronic hepatitis B, tenofovir accounted for the largest share of ADRs in our series, which likely reflects its greater use rather than excess risk per se; events were chiefly nausea, fatigue and headache, and severity was usually mild [13, 14, 15]. Entecavir recipients in our study most often reported headache without serious ADR(with occasional dizziness or nausea), a pattern consistent with its generally favourable safety profile[16, 17, 18].

For chronic hepatitis C, sofosbuvir with daclatasvir or velpatasvir produced ADRs that were largely mild fatigue, headache, nausea and a later median onset than nucleos(t)ide analogues. Large registration trials and real-world series consistently describe these same events as the commonest, with low discontinuation rates, aligning with the benign clinical course we observed.[19, 20, 21, 22]. Onset of ADR predominantly later in hepatitis C than hepatis B. Causality and severity were adjudicated using WHO-UMC and Hartwig frameworks, respectively an approach that improves reproducibility and comparability of pharmacovigilance findings. The predominance of "possible/probable" causality and "mild" severity mirrors patterns frequently seen in previous studies [12, 23, 24].

The results highlight the practical feasibility and clinical value of prospective ADR documentation. Under-reporting of ADRs is a persistent challenge globally and in India, driven by knowledge and attitudinal barriers as well as workflow constraints; integrating simple, standardised tools at the point of care , complement national pharmacovigilance databases[10, 25, 26]. Limitations are inherent to the design and setting: single-centre sample with modest numbers per drug (limiting power for between-drug comparisons), outpatient follow-up that may miss delayed or rare events.

Conclusion

Antiviral therapy led to biochemical improvement, ADRs were mostly mild to moderate, drug-specific, and occurring early with nucleos(t)ide analogues—being relatively common. Notably, significant underreporting was observed. Structured early monitoring and standardized causality/severity assessment are feasible in outpatient care, but stronger pharmacovigilance is essential to generate robust safety data in viral hepatitis

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