Rapid review of suspected ADRs due to remdesivir in the WHO database; findings and implications

Jaykaran Charan[1], Rimple Jeet Kaur[2], Pankaj Bhardwaj[3], Mainul Haque[4], Praveen Sharma[5], Sanjeev Misra[6], Brian Godman[7,8,9,10*]

[1]Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, India. dr.jaykaran78@gmail.com. ORCID ID: https://orcid.org/0000-0002-4857-6725
[2]Department of Pharmacology, S.N. Medical College, Jodhpur, India. Email: sidhurimple@yahoo.com. ORCID number: https://orcid.org/0000-0003-4478-1411
[3]Department of Community and Family Medicine. All India Institute of Medical Sciences, Jodhpur, India. Email: pankajbhardwajdr@gmail.com. ORCID number: https://orcid.org/0000-0001-9960-3060
[4]Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, 57000 Kuala Lumpur, Malaysia. Email: runurono@gmail.com. ORCID ID: https://orcid.org/0000-0002-6124-7993
[5]Department of Biochemistry, All India Institute of Medical Sciences, Jodhpur, India. Email: Email: praveensharma55@gmail.com. ORCID number: https://orcid.org/0000-0002-8324-737X
[6]Department of Surgical Oncology, All India Institute of Medical Sciences, Jodhpur, India. Email: misralko@gmail.com. ORCID number: https://orcid.org/0000-0002-0641-0946
[7]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: brian.godman@strath.ac.uk. ORCID number: http://orcid.org/0000-0001-6539-6972
[8]School of Pharmacy, Sefako Makgatho Health Sciences University, Ga-Rankuwa, Pretoria, 0208, South Africa
[9]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia
[10]Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden. Email: Brian.Godman@ki.se

*Author for correspondence: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: Brian.godman@strath.ac.uk. Telephone: 0141 548 3825. Fax: 0141 552 2562.

Abstract
Objectives: Remdesivir has shown promise in the management of patients with COVID-19 although recent studies have shown concerns with its effectiveness in practice. Despite this there is a need to document potential adverse drug events (ADEs) to guide future decisions as limited ADE data available before COVID-19 pandemic. Methods: Interrogation of WHO VigiBase® from 2015 to 2020 coupled with published studies of ADEs in COVID-19 patients. The main outcome measures are the extent of ADEs broken down by factors including age, seriousness, region and organ. Results: A total 1086 ADEs were reported from the 439 individual case reports up to 19 July 2020 in the VigiBase®, reduced to 1004 once duplicates were excluded. Almost all ADEs concerned COVID-19 patients (92.5%), with an appreciable number from the Americas (67.7%). The majority of ADEs were from males > 45 years, and were serious (82.5%). An increase in hepatic enzymes (32.1%), renal injury (14.4%), rise in creatinine levels (11.2%) respiratory failure (6.4%) were the most frequently reported ADEs. Conclusions: Deterioration of liver and kidney function are frequently observed ADEs with remdesivir; consequently, patients should be monitored for these ADEs. The findings are in line with ADEs included in regulatory authority documents.

Key highlights:

- Remdesivir is one of the proposed medicines for the treatment of the COVID – 19; however, there is paucity of data regarding its safety
- We analysed all the ADEs suspected to be caused by the remdesivir reported in WHO database in last five years

- Rise in hepatic enzymes, as well as renal injury, rises in blood creatinine, respiratory failure, tachy or bradyarrhythmia, hypotension and rashes were most frequent ADEs reported from WHO database. Similar reporting was observed in data reported from clinical trials
- Majority of these ADEs were of serious nature and many of the serious ADEs were fatal but in the absence of causality assessment these cannot be attributed to the remdesivir with certainty
- Overall, reported ADEs are in line with the ADRs reported from the clinical trials

1. Introduction

A number of medicines now have been proposed and researched for managing patients with COVID-19 [1-4]. However, to date, there appears to be no cure although dexamethasone is showing the most promise in well-constructed studies [5-7]. The earlier randomised, placebo-controlled trial in China with remdesivir involving 240 hospitalised patients with severe COVID-19 found no significantly improved clinical benefit [8]. However, it was recognized this trial was underpowered [9]. The more recent study with Beigel *et al.* (2020) found that among patients hospitalised with severe COVID-19, a 10-day course of remdesivir was associated with a faster time to recovery, with the findings were significant among patients who received oxygen. The mortality rate was 7.1% with remdesivir compared with 11.9% with placebo, although this difference was not statistically significant [10]. More recently, Goldman *et al.* (2020) showed no significant difference in outcomes between patients with severe disease prescribed either a 5 or 10-day course of remdesivir; however, this study was not placebo controlled [11]. Spinner et al (2020) have also recently shown that remdesivir has variable clinical benefit in patients with moderate COVID-19 [12], with the recent interim analysis of the WHO Solidarity study suggesting no benefit from remdesivir in reducing initiation of ventilation, duration of hospitalisation or mortality [7,13]. Consequently, further studies may still be needed to fully assess the place of remdesivir in the management of patients with COVID-19 [14].

In view of this, it is important to continue to collect safety data on the re-purposed use of remdesivir for the treatment of patients with COVID-19 alongside the collection of additional data regarding its effectiveness in patients with moderate to severe disease [15]. This is because there have been reports of serious adverse effects with remdesivir including hepatotoxicity [16], with the ability of SARS-CoV-2 to induce alterations in hepatic function potentially a particular concern when prescribing remdesivir [15,17]. This includes routine clinical care in addition to randomized studies since we are aware for instance that in the study of Beigel et al. (2020) that there were substantial exclusion criteria, e.g. AST or ALT (Alanine Aminotransferase) 5 times the upper limit of normal (ULN) and those with impaired renal function 10,17]. Renal impairment is included since urine is found to contain 49% of remdesivir's metabolite GS-441524 [18]. Similar exclusion criteria existed in the UK with respect to ALT levels and impaired renal function in the prescribing guidance issued from NHS England working with the devolved administrations, with treatment stopped if there was ALT elevation accompanied by signs or symptoms of liver inflammation or increasing alkaline phosphatase, conjugated bilirubin or international normalized ratios, as well as with the European Medicine Agency's authorization of compassionate use for remdesivir [19,20].

We are aware from data supplied by Gilead in their application to the EMA for compassionate use in patients with COVID-19 that in pooled studies ADRs were observed in < 5% of the subjects [20]. The most common ADRs in these studies, and in a controlled trial with patients with Ebola virus disease, were phlebitis, constipation, headache, ecchymosis, nausea and pain in extremities, and a transient increase in liver enzymes [20,21]. Prior to this, remdesivir was found to reversibly increase liver enzymes in healthy volunteers during early drug development studies. However, there was also a rise in liver enzymes in patients administered remdesivir in the compassionate use programme [22].

Consequently, we believed it was important to rapidly review the current status of ADEs associated with remdesivir including those emanating from published studies in patients with COVID-19. We believe this is important since even ADEs that were rare before the widespread use of remdesivir become important for patients who are hospitalized on COVID-19, especially those requiring oxygen. Further, drug-disease interactions may differ given the differences in the populations with patients with COVID-19 generally older and with co-morbidities. In view of this, we believe it is critical to characterize specific ADEs that arise for the repurposed use of remdesivir for COVID-19. The findings can further guide physicians and others in the management of patients with COVID-19 with remdesivir given some of the controversies surrounding its use. This builds on physicians in the US and wider

still being encouraged to report any adverse events relating to remdesivir to the FDA's MedWatch Safety Information and Adverse Event Reporting Program to accrue more safety data especially with more clinical trials needed to fully assess the place of remdesivir in the management of patients with COVID-19 [14,23].

2. Patients and Methods

This principally involved interrogating the VigiBase®, which is the global pharmacovigilance database maintained by the WHO, and previously used to evaluate ADEs associated with hydroxychloroquine [24,25]. VigiBase® contains all ICSRs of adverse events collected by the national pharmacovigilance centers from over 130 countries [26-28]. An ICSR is an anonymised report for a single individual (patient) who was given suspected drug, who experienced single or multiple ADEs.

VigiBase® contains reports in a structured form containing information regarding patient demographics, drugs (route of administration, indication for use, start, end date), suspected ADEs (date of onset, outcome, seriousness, and causality), and administrative data (type of report and source). Medicines are coded according to the WHO Drug Dictionary Enhanced, including the ATC (Anatomical Therapeutic Chemical) classification [29]. Adverse events are coded according to the WHO Adverse Reaction Terminology and the Medical Dictionary for Regulatory Authorities (MedDRA) [25,30]. The MedDRA dictionary is organized by System Organ Class (SOC), divided into Preferred Terms (PT), and Lowest-Level Terms (LLT).

2.1 Data and Analysis
This study included the analysis of all suspected adverse events related to remdesivir notified in last 5 years to VigiBase®, i.e. from 1st January 2015 2015 to 19th July 2020. Each report in VigiBase® referred to a single individual who may have encountered one or several adverse events simultaneously. Consequently, the number of reported adverse events is typically higher than the number of patients for whom the case reports were recorded. ADRs were again classified following the Medical Dictionary for Regulatory Authorities (MedDRA); grouped at the System Organ Classification (SOC) level and at the individual preferred term (PT) level. The System Organ Classification, i.e. the SOC, is a grouping of individual ADEs coded in pre fix preferred terms into the different headings based on aetiology, e.g. infections and infestations, manifestation site, e.g. hepatobiliary disorders, purpose, e.g. surgical and medical procedures, product issues and social circumstances.

The reports were analysed on the basis of age, gender, region of reporting, organ classification (SOC) level and at the individual preferred term (PT) level category of adverse event, seriousness, outcome, dechallenge–rechallenge action and outcome. With respect to age, we chose before and after 64 years of age as mortality with COVID-19 rises with age [31-33]. The seriousness of the ADE was decided based on ICH E2B criteria in which ADEs leading to the following conditions are categorized as serious ADEs – Death, life threatening, require hospitalization, prolongation of hospitalization lead to disability or congenital anomaly [34,35]. Data cleaning was performed manually and same ADEs reported in different terminology from the same case information reports were removed to prevent multiple counting. Reporting of the same ADE by different terms happens due to multiple reporting of the same ADEs by different stakeholders i.e. physicians, nursing professionals and pharmacists.

Reporting of death was not clear in the database that was shared with us. We subsequently inquired about this from the database administrators. Following the guidance received from them, death reported in any of the heading "seriousness", "outcome" and "preferred term" were considered for the calculation of the death.

Descriptive statistics was reported in the form of frequency and percentages. The Statistical Package for Social Science (SPSS) Version 21 was used for the analysis.

2.2 Published and other studies regarding adverse events seen with remdesivir

Alongside documenting the ADEs seen with remdesivir in the VigiBase®, we also sought to document ADEs contained within published studies as well as submissions by Gilead to the regulatory authorities to compare and contrast the findings.

We are aware that age and other factors can play a role in the extent of ADEs [36-38], which is a concern if such factors have not been included in trial design or analysis. There is also a concern with new medicines generally as clinical trials tend to include carefully selected patients, who are generally younger and less co-morbid than those treated in routine clinical care [39,40]. Consequently, we believe it is critical to analyse both spontaneous reports with remdesivir alongside data from the clinical trials to provide future guidance given current concerns.

3. Results

We will first summarise reported ADEs in the published studies as well as summaries provided by Gilead to the regulatory authorities before documenting the ADEs reported to VigiBase®.

3.1. Summary of reported ADEs in published and other documents

Table 1 summarises the findings form published and other sources including submissions to the various regulatory authorities.

Table 1 – Summary of ADEs seen with remdesivir

Source and year	Patient categories	Findings
Mulangu et al (2019) [21]	Randomised trial of 681 patients testing positive for Ebola virus the on reverse-transcriptase–polymerase-chain-reaction assay	• 29 serious AEs were determined by trial investigators to be potentially related to the trial drugs • After adjudication by an independent panel, 4 events in 3 patients, all resulting in death, were possibly related to trial drugs. This included one patient in the remdesivir group who had hypotension that resulted in cessation of a loading dose of remdesivir followed rapidly by cardiac arrest - however, could not be readily distinguishable from underlying Ebola • Typically, the safety profile was generally consistent with Phase 1 data
EMA summary for compassionate use (2020) [20]	AE data from 131 patients in Gilead sponsored studies	The following was found to occur in 5 or more subjects: • Phlebitis – 8 patients • Constipation – 7 patients • Headache – 6 patients • Ecchymosis, nausea, and pain in extremities – 5 patients each
Grein et al (2020) [41]	Analysis of data from 53 patients with severe COVID-19 enrolled into a compassionate use programme	32 patients (60%) reported ADEs. These included: • Hepatic enzyme increases - 23% of patients • Diarrhoea – 9% of patients • Renal impairment, rash, hypotension - 8% of patients • Acute kidney injury, multiple organ dysfunction syndrome, hypernatremia, DVT - 6% of patients • Serious ADEs occurred in 23% of patients with 8% discontinuing remdesivir due to side effects
Wang et al (2020) [8]	237 patients with severe COVID-19 enrolled and randomly assigned to remdesivir (158 patients) or placebo (79 patients)	• ADEs were reported in 66% of patients in the remdesivir group and 64% in the control • The most common ADEs in the remdesivir group were constipation (14%), hypoalbuminaemia (13% - none severe), hypokalaemia (12% - 1% severe), anaemia (12% - 1% severe), thrombocytopenia (19% - 3% severe), and increased total bilirubin (10% - 1% severe)

		• 28 patients in the remdesivir group (18%) had serious ADEs with more patients in the remdesivir group discontinuing treatment due to ADEs • All deaths during the observation period were judged to be unrelated to the intervention

Goldman et al (2020) [11]	397 patients with severe COVID-19 randomized to either 5 days treatment (200 patients) or 10 days treatment (197 patients)	• 70% of patients int he 5-day group and 74% in the 10-day group experienced ADEs, with 21% in the 5-day group and 35% in the 10-day group experiencing serious ADEs
		• The most common ADEs were:
		   o Nausea - 10% in the 5-day group and 9% in the 10-day group
		   o Acute respiratory failure - 6% in the 5-day group and 11% in the 10-day group
		   o Increased ALT - 6% in the 5-day group and 8% in the 10-day group
		   o Constipation - 7% in both groups
		• 4% in the 5-day group discontinued treatment owing to ADEs versus 10% in the 10-day group

Biegel et al (2020) [10]	1062 hospitalised patients with COVID-19 randomised either to remdesivir or placebo	• Serious ADEs occurred in 24.6% of patients in the remdesivir group vs. 31.6% in the placebo group • 8.8% of patients in the remdesivir group had serious respiratory failure AEs including acute respiratory failure and the need for endotracheal intubation • No deaths were considered by the investigators to be related to treatment assignment • The most common nonserious ADEs occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin levels and lymphocyte counts, respiratory failure, anemia, pyrexia, and hyperglycemia as well as increased blood creatinine levels and blood glucose levels. The incidence of AEs was generally similar between the remdesivir and placebo groups
Spinner et al (2020) [12]	Study of 596 patients with moderate COVID-19 randomised to either 5 or 10 days of treatment with remdesivir vs. standard care	• AEs were experienced by 51% of patients in the 5-day remdesivir group vs. 59% in the 10-day remdesivir group and 47% in the standard care group • Differences between the 5-day remdesivir group and standard care was not statistically significant but the difference between the 10-day remdesivir group and standard care were • AEs more common in the remdesivir groups vs. standard care included nausea (10% 5-day and 9% 10-day groups), hypokalemia (5% 5-day and 7% 10-day), and headaches (5% both groups). Diarrhoea also occurred but 6% in 5-day group, 5% in 10-day group and 7% in standard care group • Serious AEs were less common in the remdesivir groups (5% in both) vs. standard care (9%)

			• Deaths occurred in the remdesivir group (but also standard care group) but none were attributed to remdesivir

3.2 Summary of findings from VigiBase®

There were a total 1087 ADEs reported from the 439 case information reports. Each case information report represents one person who was given remdesivir. After removal of duplicate ADEs (same ADE reported in different terminologies) from each case information report, 1004 unique ADEs were available for the analysis (Table 1). As multiple ADEs were often reported for each patient, the number of ADEs were appreciably more than number of persons. Overall, 1004 ADEs were reported from 439 people, giving an average 2.28 ADEs per person. Out of these 439 Individuals, 145 (33%) were from Europe, 288 (65%) from the region of Americas and 6 (1.3%) from the western pacific region. 267 (61%) were males and 163 (37.1%) were females, with gender not reported for 9 (2%) individuals. However, the majority of ADEs came from persons in the Americas (680 – 67.7%)

Table 2 represents the characteristics of 1004 ADEs reported in the WHO database. All these are unique ADEs reported from 439 individuals. It was noted that around half of the ADEs were reported from the age group 18 to 64. More ADEs were reported from males than females (58.9%) and the majority of the ADEs were serious. Indications for the use of remdesivir for almost all cases was COVID – 19 infection (92.6%), with 5.8% ADEs fatal. Parameters to assess the causality i.e. dechallenge action, dechallenge outcome, rechallenge action and rechallenge outcome was reported for a minority of the ADEs. However, as complete data was typically lacking assessment of causality was not possible.

Table 2: Characteristics of Adverse Drug Events (N =1004 ADEs) reported from 439 Individuals reported for remdesivir in WHO database

Parameter		Frequency (%)
Age	< 18 Years	21 (2.1)
	18 – 64 Years	469 (46.7)
	≥ 65 Years	417 (41.5)
	Not reported	97 (9.7)
Gender	Female	399 (39.7)
	Male	591 (58.9)
	Not reported	14 (1.4)
Continents	Americas	680 (67.7)
	Asia	7 (0.7)
	Europe	314 (31.3)
	Oceania	3 (0.3)
Report Type	Report from study	249 (24.8)
	Spontaneous	755 (75.2)
Seriousness of Adverse Event	Serious	828 (82.5)
	Non-Serious	176 (17.5)
Route of Administration	Intravenous	805 (80.2)
	Iontophoresis	8 (0.8)
	Respiratory (inhalation)	3 (0.3)
	Other	1 (0.1)
	Unknown	53 (5.3)
	Not reported	134 (13.4)
Indication for use	Covid-19 treatment	930 (92.6)
	Acinetobacter infection	2 (0.2)
	ARDS	1 (0.1)
	Drug use for unknown indication	5 (0.5)
	Not reported	66 (6.5)
Outcome	Fatal	58 (5.8)
	Not recovered/not resolved	122 (12.2)
	Recovered/resolved	101 (10.1)
	Recovered/resolved with sequelae	1 (0.1)
	Recovering/resolving	30 (3.0)
	Unknown	93 (9.7)
	Not reported	599 (59.7)
Dechallenge Action	Dose not changed	122 (12.2)
	Drug withdrawn	221 (22.0)
	Not applicable	25 (2.5)
	Unknown	35 (3.5)
	Not reported	601 (59.9)

Parameter		Frequency (%)
Dechallenge Outcome	Fatal	57 (5.7)
	No effect observed	120 (12.0)
	Reaction abated	132 (13.2)
	Effect unknown	93 (9.3)
	Not Reported	602 (60.0)
Rechallenge Action	Rechallenge	133 (13.2)
	Not Reported	871 (86.8)
Rechallenge Outcome	Effect unknown	106 (10.6)
	No recurrence	27 (2.7)
	Not Reported	871 (86.8)

An increase in liver enzymes was most frequent ADEs suspected to be caused by remdesivir. Overall, approximately one third of the patients who were given remdesivir, reported increase in liver enzyme (Table 3). However, it was not possible to pin point which liver enzyme was most frequently increased due to the unavailability of such data in many of the case information reports. Kidney related ADEs were also frequent as there were many reports of renal injury (14.4%), rise in blood creatinine (11.2%), renal impairment and a decrease in glomerular filtration rate (3.2%). Respiratory failure, arrhythmia, hypotension and rash were also commonly reported ADEs (Table 2). All 1004 ADEs reported from the 439 individuals are mentioned in Appendix 1.

Table 3: Top 25 ADEs suspected to be caused by remdesivir reported in 439 individuals in WHO database (N = 439)

Sl. No.	ADEs	Frequency (%)
1	Hepatic enzyme increased	141 (32.11)
2	Renal Injury	63 (14.4)
3	Blood creatinine increased	49 (11.2)
4	Medication Error	34 (7.7)
5	Product Use in Unapproved Condition	29 (6.6)
6	Respiratory failure	28 (6.4)
7	Tachy or Bradyarrythmia	26 (5.9)
8	Hypotension	24 (5.5)
9	Rash	22 (5.0)
10	Therapy cessation	22 (5.0)
11	Condition Aggravated/Disease Progression	19 (4.3)
12	Sepsis and Septic Shock	18 (4.1)
13	Cardiac and Cardiorespiratory Arrest	17 (3.9)
14	Nausea/Vomiting	15 (3.4)
15	Glomerular filtration rate decreased	14 (3.2)
16	Renal impairment	14 (3.2)
17	Abnormal Hemogram	13 (3.0)
18	Renal failure	13 (3.0)
19	Death	12 (2.7)
20	Multiorgan Disorder/Organ Failure	11 (2.5)
21	Pyrexia	11 (2.5)

22	Hypoxia	11 (2.5)
23	Dialysis	11 (2.5)
24	Diarrhea	10 (2.3)
25	Acidosis	10 (2.3)

On comparing some important characteristic of ADEs of persons between ages < 64 and > 64, it was observed that serious and fatal ADEs were more often reported in the older age group. ADEs related to investigations were more common in the younger age group i.e. age < 64 in comparison to the age group > 64 (34% vs. 21%). ADEs related to renal and urinary disorders were more often seen in the older age group i.e. > 64 as compared to the younger age group, i.e. < 64 (14% vs. 7%) (Table 4).

Table 4: Comparison of ADEs of remdesivir between the age groups less and more than 64 years of age (N = 1004)

Parameters		Age < 64 (N=485)	Age 64 & Above (N = 417)	Age Unknown (N = 97)
Seriousness				
	Serious (N = 828)	384 (79.2)	373 (89.4)	71 (73.2)
	Non serious (N = 176)	106 (21.8)	44 (10.6)	26 (26.8)
ADR organ system				
	Blood and lymphatic system disorders (N=20)	8 (1.6)	7 (1.7)	5 (5.2)
	Cardiac disorders (N=51)	22 (4.5)	27 (6.5)	2 (2.1)
	Ear and labyrinth disorders (N = 1)	1 (0.2)	0	0
	Eye disorders (N=6)	2 (0.4)	0	4 (4.1)
	Gastrointestinal disorders (N=42)	22 (4.5)	16 (3.8)	4 (4.1)
	General disorders and administration site conditions (N = 84)	39 (8.0)	40 (9.6)	5 (5.2)
	Hepatobiliary disorders (N = 23)	10 (2.1)	8 (1.9)	5 (5.2)
	Immune system disorders (N = 1)	1 (0.2)	0	0
	Infections and infestations (N = 36)	16 (3.3)	16 (3.8)	4 (4.1)
	Injury, poisoning and procedural complications (N = 73)	36 (7.4)	28 (6.7)	9 (9.3)
	Investigations (N = 283)	165 (34.0)	88 (21.1)	30 (30.9)
	Metabolism and nutrition disorders (N = 22)	11 (2.3)	8 (1.9)	3 (3.1)
	Musculoskeletal and connective tissue disorders (N = 5)	0	3 (0.7)	2 (2.1)
	Nervous system disorders (N = 34)	11 (2.3)	21 (5.0)	2 (2.1)
	Psychiatric disorders (N = 10)	3 (0.6)	7 (1.7)	0
	Renal and urinary disorders (N = 102)	35 (7.2)	58 (13.9)	9 (9.3)
	Reproductive system and breast disorders (N = 1)	1 (0.2)	0	0
	Respiratory, thoracic and mediastinal disorders (N = 89)	35 (7.2)	49 (11.8)	5 (5.2)
	Skin and subcutaneous tissue disorders (N = 36)	24 (4.9)	7 (1.7)	5 (5.2)
	Social circumstances (N =1)	0	1 (0.2)	0
	Surgical and medical procedures (N = 41)	23 (4.7)	17 (4.1)	1 (1.0)

	Vascular disorders (N =43)	25 (5.2)	16 (3.8)	2 (2.1)
Outcome	Fatal (N =58)	9 (1.9)	42 (10.1)	7 (7.2)
	Not recovered/Not resolved (N =122)	67 (13.8)	19 (4.6)	36 (37.1)
	Recovered/Resolved (N =101)	62 (12.8)	15 (3.6)	24 (24.7)
	Recovered/Resolved with sequelae (N =1)	0	0	1 (1.0)
	Recovering/Resolving (N =30)	11 (2.3)	10 (2.4)	9 (9.3)
	Unknown (N =93)	50 (10.3)	25 (6.0)	18 (18.6)
	Not Reported (N =599)	291 (6)	306 (73.4)	2 (2.1)

NB: Values in parenthesis are percentages. The denominator for the percentages are people in each age category.

Serious ADEs were more often seen in males in comparison to the females (59% Vs 40%). Cardiac, renal and respiratory ADEs were more frequently reported as serious as compared to other ADEs (Table 5).

Table 5: Comparison of serious and non-serious ADEs for various characteristics (N = 1004)

Parameters		**Serious (N = 828)**	**Non Serious (N = 176)**
Gender	Male (N = 591)	490 (59.2)	101 (57.4)
	Female (N = 399)	332 (40.1)	67 (38.1)
	Gender Not mentioned (N =14)	6 (0.7)	8 (4.5)
System involved in ADR	Blood and lymphatic system disorders (N = 20)	16 (1.9)	4 (2.3)
	Cardiac disorders (N = 51)	48 (5.8)	3 (1.7)
	Ear and labyrinth disorders (N = 1)	1 (0.1)	0
	Eye disorders (N = 6)	2 (0.2)	4 (2.3)
	Gastrointestinal disorders (N = 42)	33 (4.0)	9 (5.1)
	General disorders and administration site conditions (N = 84)	71 (8.6)	13 (7.2)
	Hepatobiliary disorders (N = 23)	19 (2.3)	4 (2.3)
	Immune system disorders (N = 1)	1 (0.1)	0
	Infections and infestations (N = 36)	32 (3.9)	4 (2.3)
	Injury, poisoning and procedural complications (N = 73)	41 (5.0)	32 (18.2)
	Investigations (N = 283)	221 (26.7)	62 (35.2)
	Metabolism and nutrition disorders (N = 22)	17 (2.1)	5 (2.8)
	Musculoskeletal and connective tissue disorders (N = 5)	5 (0.6)	0
	Nervous system disorders (N = 34)	32 (3.9)	2 (1.1)
	Psychiatric disorders (N = 10)	4 (0.5)	6 (3.4)
	Renal and urinary disorders (N = 102)	99 (12.0)	3 (1.7)
	Reproductive system and breast disorders (N = 1)	1 (0.1)	0
	Respiratory, thoracic and mediastinal disorders (N = 89)	85 (10.3)	4 (2.3)

	Skin and subcutaneous tissue disorders (N = 36)	25 (3.0)	11 (6.3)
	Social circumstances (N = 1)	1 (0.1)	0
	Surgical and medical procedure (N = 41)	35 (4.23)	6 (3.4)
	Vascular disorders (N = 43)	39 (4.7)	4 (2.3)
Outcome	Fatal (N = 58)	58 (7.0)	0
	Not recovered/not resolved (N = 122)	98 (11.8)	24 (13.6)
	Recovered/resolved (N = 101)	66 (8.0)	35 (19.9)
	Recovered/resolved with sequelae (N = 1)	0	1 (0.6)
	Recovering/resolving (N = 30)	23 (2.3)	7 (4.0)
	Unknown (N = 93)	80 (9.7)	13 (7.2)
	Not Mentioned (N = 599)	502 (60.6)	96 (54.6)

NB: Values in parenthesis are percentages. The denominator for the percentages are the frequency of serious and non-serious ADEs.

87 deaths were reported. The majority of these were in people aged > 64 and male gender. The most common immediate reasons for death were multiple organ dysfunction, cardiac, cardio-respiratory and respiratory arrest (Table 6).

11

TABLE 6: Characteristics of deaths reported for remdesivir in WHO database (N=87)

PARAMETER		FREQUENCY (%)
Age	Age below 64	25 (28.7)
	Above 64	56 (64.4)
	Unknown	6 (6.9)
WHO Region	Region of America	60 (69.0)
	Europe	26 (29.9)
	Western Pacific Region	1 (1.2)
Gender	Female	30 (34.5)
	Male	57 (65.5)
Adverse Drug Event System Involved (Top 5)	General disorders and administration site conditions	23 (26.4)
	Cardiac disorders	20 (23.0)
	Respiratory, thoracic and mediastinal disorders	11 (12.6)
	Infections and infestations	11 (12.6)
	Blood and lymphatic system disorders	4 (4.6)
Adverse Drug Event (Top 5)	Multiple organ dysfunction syndrome	8 (9.2)
	Cardiac arrest	8 (9.2)
	Cardio-respiratory arrest	6 (6.9)
	Respiratory failure	5 (5.8)
	Condition aggravated	4 (4.6)

4. Discussion

We believe this is one of the first studies post COVID-19 pandemic to appraise the nature and extent of remdesivir ADEs in WHO database following its repurposing for COVID-19, building on the published studies (Table 1). We believe this is important given some of the controversies surrounding treatments for patients with COVID-19 including remdesivir [6,7,12,42]. In additon, the differences in the nature of the COVID-19 population compared to those patients typically receiving remdesivir before the COVID-19 pandemic.

It was observed that the majority of ADEs were reported from male subjects and those aged 45 years or greater (Table 2). The majority of events were reported from the American continent, and were spontaneously reported by health professionals (Table 2). This may reflect the fact that almost all ADEs were for the management of patents with COVID-19 (92.6%), the high profile NIH study with remdesivir, endorsement of remdesivir by the US FDA, and moves by the USA government to stockpile supplies limiting their availability initially to other countries [43-45]. Just under a third of the reports were from Europe, perhaps again reflecting initial endorsement from the European Medicine Agency and others for compassionate use [19,46,47]. However, further research is needed before we can make any definitive statements. We are aware though that there have been concerns with the extent of ADE reporting in a number of countries, especially lower- and middle-income countries (LMICs) in recent years, which may have impacted on the extent of reports outside of Europe and the US [48-52]. Improvements in ADE and ADR reporting are needed across countries generally and especially with new medicines, with educational and other initiatives known to be successful [53-55].

The majority of the ADEs were related to investigations followed by renal, urinary and respiratory disorders (Tables 3 and 4). An increase in hepatic enzymes and kidney injury were the principal individual ADEs (Table 2) reflecting findings in the published studies, with more non-serious ADEs

found in the younger age group, i.e. < 64 (Tables 4 and 5). Serious ADEs were found more in males (Table 5) and, as expected, fatal and not recovered/resolved events were found more in those patients with serious ADEs (Table 5 and 6). The main individual reasons for the death was multiple organ failure and cardiac arrest (Table 6), again reflecting some of the published literature.

An increase in hepatic enzymes is a concern with the administration of remdesivir. To address this, the product information for remdesivir suggests that liver function tests should be performed before starting remdesivir and that remdesivir should not be given to the patients having ALT levels more than 5 times normal levels, ALT increases associated with signs and symptoms of liver inflammation or with an increase in other liver enzymes [22]. Consequently, we believe it is important for physicians to keep tracking patient's liver function during treatment with remdesivir as suggested in the product summary information. However, we are currently unaware of any guidance regarding the need for dose adjustments of remdesivir in patients with hepatic impairment. Consequently, physicians will need to decide to initiate or continue the use of remdesivir in such patients based on their perceived risk benefit ratio.

Kidney injury and dysfunction is seen as another major ADE associated with remdesivir (Tables 3 and 5, Appendix). However, we are aware that kidney dysfunctions have been observed in the control arm of the clinical trials indicating that the disease process itself may be associated with these ADEs. We believe that up to now remdesivir has not been systematically assessed in patients with severe renal impairment or end stage renal failure, which is a concern that needs to be addressed with more widespread use. However, before initiating remdesivir the GFR should be measured in adults, and > 28 days old paediatric patients, and this should be > 30 ml/min. In the case of paediatric patients age < 28 days, serum creatinine should be measured, and this should be more than 1 mg/dl [23]. The remdesivir formulation also has the excipient sulfobutylether β cyclodextrin (SBECD), which is cleared in the kidneys and accumulates when GFR is low. Consequently, we recommend that the renal function of patients with COVID-19 is assessed before initiation of remdesivir to prevent any toxicity due to SBECD affecting treatment decisions [56,57]. Overall, renal function is a concern with remdesivir, and should be closely monitored with limited improvement following withdrawal [23].

Overall, there is a need to continually monitor ADEs arising from remdesivir to provide future guidance. There is a role for Drug and Therapeitic Committess (DTCs) in hospitals to enhance ADE reporting as well as continue to promote evidence-based medicine (EBM) to optimise treatment for patients with COVID-19 and other diseases [53,58-60]. This includes updating physicians on the effectiveness and safety of remdesivir as new information becomes available in line with activities and recommendations for managing the entry of new medicines into clinical care as seen with new anticoagulants and new medicines for patients with hepatitis C [61-64].

We are aware of a number of limitations with this study. Firstly, this study is based on VigiBase, which is a global database of individual case safety reports. The individual case safety reports in this database come from different sources and information emanating from this database should not be taken as the opinion of Uppsala Monitoring Centre or World Health Organization. Secondly, there may be ADEs which are less frequent that can only be observed in large dataset. Thirdly, there is also no absolute certainty about the causality for the reported ADEs especially as many characteristics of COVID-19 are still unknown and the disease itself is associated with considerable morbidity and mortality in some patients. In addition, data obtained from the VigiBase® does not typically include an overall judgement about the causality of ADEs but does report a few components deciding about causality i.e. dechallenge action, dechallenge out, rechallange action and rechallenge outcomes as depicted in our analysis. However, if at least one component for these data is missing, which was the case in almost all the reports in our study, such data cannot be incorporated into the analysis. We have also not undertaken any comparisons based on statistical tests to prevent bias arising from missing/ unavailable data for any variable. We are also aware it would have been worthwhile to compare the ADEs reported for remdesivir before and after COVID – 19 especially given likely differences in the patient characteristics; however, this was not possible because no ADE was reported to Vigibase® between 2015 and 2019 possibly due to infrequent use before the COVID-19 pandemic. There may have been some ADEs reported before 2015; however, this was outside the scope of this study. All the ADEs included in the analysis were those in which remdesivir was suspected. We have not incorporated in our analysis any ADEs where remdesivir was concomitantly given but was not suspected. We are aware the WHO receives information on ICSRs from numerous sources; consequently, there is a probability that suspected adverse effects is drug-related is not the

same in all cases. However, despite these limitations, we believe it is helpful to consolidate current knowledge regarding potential ADEs from remdesivir and possible ways to address these. The findings and their interpretation can be added to as more data becomes available.

5. Conclusion

This study was an attempt to descriptively analyse ADEs reported to date for remdesivir to add to the information about the safety of remdesivir reported to date from published clinical trials in patients with COVID-19 given potential concerns. The most important ADEs were elevation of liver enzymes and those arising from kidney injury, which is in line with the product information given by the FDA. These findings call for greater monitoring of liver enzymes during treatment, building on existing guidance, with the potential for dose adjustments, as well as monitoring renal function before and during treatment with remdesivir. Greater guidance can also be given by the authorities as more knowledge becomes available including potential doses of remdesivir in patients with COVID-19 with existing hepatic impairment or poor renal function.

Conflicts of interest and funding

This study was self funded and the authors declare they have no conflicts of interest.

References
(*of interest; **of considerable interest)
1.   Jan H, Faisal S, Khan A, Khan S, Usman H, Liaqat R, et al. COVID-19: Review of Epidemiology and Potential Treatments Against 2019 Novel Coronavirus. Discoveries (Craiova, Romania). 2020;8(2):e108.
2.   Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. Jama. 2020.
3.   Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Critical care. 2020;24(1):91.
4.   Scavone C, Brusco S, Bertini M, Sportiello L, Rafaniello C, Zoccoli A, et al. Current pharmacological treatments for COVID-19: what's next? British journal of pharmacology. 2020.
5.   Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.
6.   Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020;396(10259):1345-52.
7.   WHO Solidarity trial consortium. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. MedRxiv (October 15) version available at URL: https://doi.org/10.1101/2020.10.15.20209817
8.   Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-78.
9.   BMJ Best Practice - Coronavirus disease 2019 (COVID-19). 30 July 2020. Available at URL: https://bestpractice.bmj.com/topics/en-gb/3000168/pdf/3000168/Coronavirus%20disease%202019%20%28COVID-19%29.pdf.
10.   Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020.
**Landmark study documenting the impact of remdesivir in patients with COVID-19
11.   Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020.
12.   Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama. 2020;324(11):1048-57.
*Key paper documenting the effect of remdesivir on patients with moderate COVID-19
13.   Dyer O. Covid-19: Remdesivir has little or no impact on survival, WHO trial shows. BMJ (Clinical research ed). 2020;371:m4057.
14.   McCreary EK, Angus DC. Efficacy of Remdesivir in COVID-19. Jama. 2020;324(11):1041-2.
15.   Jorgensen SCJ, Kebriaei R, Dresser LD. Remdesivir: Review of Pharmacology, Pre-clinical Data, and Emerging Clinical Experience for COVID-19. Pharmacotherapy. 2020;40(7):659-71.
16.   Lam S, Lombardi A, Ouanounou A. COVID-19: A review of the proposed pharmacological treatments. Eur J Pharmacol. 2020;886:173451-.

17.   Frega G, Palloni A, Di Pasquale G, Saccoccio G, Rizzo A, Poluzzi E, et al. Challenges in Repurposing Drugs in COVID-19 Pandemic. Debating on Potential New Refinements. Frontiers in pharmacology. 2020;11(1508).

18.   Singh AK, Singh A, Singh R, Misra A. Remdesivir in COVID-19: A critical review of pharmacology, pre-clinical and clinical studies. Diabetes & metabolic syndrome. 2020;14(4):641-8.

19.   NHS UK. Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older). July 2020. Available at URL; https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/07/C0654-uk-interim-clinical-commissioning-policy-remdesivir-for-patients-hospitalised-with-covid-19-adults-and-c.pdf?UNLID=5719721020200722184258.

20.   EMA. Summary on compassionate use Remdesivir Gilead - International Non-proprietary Name: remdesivir. Procedure No. EMEA/H/K/005622/CU. 3 April 2020. Available at URL: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf.

21.   Mulangu S, Dodd LE, Davey RT, Jr., Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019;381(24):2293-303.

22.   US FDA. FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir). 2020. Available at URL: https://www.fda.gov/media/137566/download

23.   Clinical Oncology News. FDA Warns of Remdesivir Drug Interaction, 17 June 2020. Available at URL: https://www.clinicaloncology.com/COVID-19/Article/06-20/FDA-Warns-of-Remdesivir-Drug-Interaction-/58782.

24.   Montastruc JL, Rousseau V, Durrieu G, Bagheri H. Serious adverse drug reactions with hydroxychloroquine: a pharmacovigilance study in Vigibase®. European journal of clinical pharmacology. 2020:1-2.

25.   Ogar CK, Abiola A, Yuah D, Ibrahim A, Oreagba IA, Amadi EC, et al. A Retrospective Review of Serious Adverse Drug Reaction Reports in the Nigerian VigiFlow Database from September 2004 to December 2016. Pharmaceut Med. 2019;33(2):145-57.

26.   Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, et al. Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events in Patients With Cancer. JAMA oncology. 2020;6(6):1-7.

27.   Vollmer O, Felten R, Mertz P, Lebrun-Vignes B, Salem JE, Arnaud L. Characterization of auto-immune hepatitis associated with the use of anti-TNFα agents: An analysis of 389 cases in VigiBase. Autoimmunity reviews. 2020;19(3):102460.

28.   Chrétien B, Lelong-Boulouard V, Chantepie S, Sassier M, Bertho M, Brazo P, et al. Haematologic malignancies associated with clozapine v. all other antipsychotic agents: a pharmacovigilance study in VigiBase(®). Psychological medicine. 2020:1-8.

29.   WHO. WHO Collaborating Centre for Drug Statistics Methodology. ATC/ DDD Index. Available at URL: https://www.whocc.no/ [

30.   Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20(2):109-17.

31.   Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5).

32.   Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

33.   Mikami T, Miyashita H, Yamada T, Harrington M, Steinberg D, Dunn A, et al. Risk Factors for Mortality in Patients with COVID-19 in New York City. J Gen Intern Med. 2020:1-10.

34.   Uppsala Monitoring Centre. Individual Case Safety Reports and VigiBase – the vital importance of quality. 2012. Available at URL: https://www.who-umc.org/media/163807/vigibase-the-vital-importance-of-quality-2017.pdf.

35.   INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE - ICH HARMONISED TRIPARTITE GUIDELINE. MAINTENANCE OF THE ICH GUIDELINE ON CLINICAL SAFETY DATA MANAGEMENT: DATA ELEMENTS FOR TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS E2B(R2). 2001. Available at URL: https://admin.ich.org/sites/default/files/inline-files/E2B_R2_Guideline.pdf.

36.   Wu T-Y, Jen M-H, Bottle A, Molokhia M, Aylin P, Bell D, et al. Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009. Journal of the Royal Society of Medicine. 2010;103(6):239-50.
*Key study documenting the impack of age on ADRs
37.   Ruiter R, Visser LE, Rodenburg EM, Trifiró G, Ziere G, Stricker BH. Adverse drug reaction-related hospitalizations in persons aged 55 years and over: a population-based study in the Netherlands. Drugs & aging. 2012;29(3):225-32.
38.   Rydberg DM, Mejyr S, Loikas D, Schenck-Gustafsson K, von Euler M, Malmström RE. Sex differences in spontaneous reports on adverse drug events for common antihypertensive drugs. European journal of clinical pharmacology. 2018;74(9):1165-73.
39.   Malmstrom RE, Godman BB, Diogene E, Baumgartel C, Bennie M, Bishop I, et al. Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs. Frontiers in pharmacology. 2013;4:39.
40.   Joppi R, Cinconze E, Mezzalira L, Pase D, Poggiani C, Rossi E, et al. Hospitalized patients with atrial fibrillation compared to those included in recent trials on novel oral anticoagulants: a population-based study. European journal of internal medicine. 2013;24(4):318-23
*Interesting study documenting the differences in ages of populations receiving new oral anticoagulants in the clinical trials versus routine clinical care
41.   Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020;382(24):2327-36.
42.   Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020.
**Landmark study documenting concerns with hydroxychloroquine
43.   Boseley. US secures world stock of key Covid-19 drug remdesivir. 30 June 2020. Available at URL: https://www.theguardian.com/us-news/2020/jun/30/us-buys-up-world-stock-of-key-covid-19-drug.
44.   FDA. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. 1 May 2020. Available at URL: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.
45.   US Department of Health and Human Services. Trump Administration Secures New Supplies of Remdesivir for the United States. 29 June 2020. Available at URL: https://www.hhs.gov/about/news/2020/06/29/trump-administration-secures-new-supplies-remdesivir-united-states.html.
46.   ECDC. ECDC - Vaccines and treatment of COVID-19. 30 June 2020. Available at URL: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/vaccines-and-treatment.
47.   EMA. First COVID-19 treatment recommended for EU authorisation. 25 June 2020. Available at URL: https://www.ema.europa.eu/en/news/first-covid-19-treatment-recommended-eu-authorisation.
48.   Lopez-Gonzalez E, Herdeiro MT, Pineiro-Lamas M, Figueiras A. Effect of an educational intervention to improve adverse drug reaction reporting in physicians: a cluster randomized controlled trial. Drug Saf. 2015;38(2):189-96.
49.   Haines HM, Meyer JC, Summers RS, Godman BB. Knowledge, attitudes and practices of health care professionals towards adverse drug reaction reporting in public sector primary health care facilities in a South African district. European journal of clinical pharmacology. 2020.
50.   Adisa R, Omitogun TI. Awareness, knowledge, attitude and practice of adverse drug reaction reporting among health workers and patients in selected primary healthcare centres in Ibadan, southwestern Nigeria. BMC health services research. 2019;19(1):926.
51.   Mulchandani R, Kakkar AK. Reporting of adverse drug reactions in India: A review of the current scenario, obstacles and possible solutions. The International journal of risk & safety in medicine. 2019;30(1):33-44.
52.   Ergün Y, Ergün TB, Toker E, Ünal E, Akben M. Knowledge attitude and practice of Turkish health professionals towards pharmacovigilance in a university hospital. Int Health. 2019;11(3):177-84.
53.   Terblanche A, Meyer JC, Godman B, Summers RS. Impact of a pharmacist-driven pharmacovigilance system in a secondary hospital in the Gauteng Province of South Africa. Hospital practice (1995). 2018;46(4):221-8.
54.   Opadeyi AO, Fourrier-Réglat A, Isah AO. Educational intervention to improve the knowledge, attitude and practice of healthcare professionals regarding pharmacovigilance in South-South Nigeria. Therapeutic advances in drug safety. 2019;10:2042098618816279.

55.   Fang H, Lin X, Zhang J, Hong Z, Sugiyama K, Nozaki T, et al. Multifaceted interventions for improving spontaneous reporting of adverse drug reactions in a general hospital in China. BMC Pharmacol Toxicol. 2017;18(1):49.

56.   Kim SH, Kwon JC, Park C, Han S, Yim DS, Choi JK, et al. Therapeutic drug monitoring and safety of intravenous voriconazole formulated with sulfobutylether β-cyclodextrin in haematological patients with renal impairment. Mycoses. 2016;59(10):644-51.

57.   Hoover RK, Alcorn H, Jr., Lawrence L, Paulson SK, Quintas M, Luke DR, et al. Clinical Pharmacokinetics of Sulfobutylether-β-Cyclodextrin in Patients With Varying Degrees of Renal Impairment. Journal of clinical pharmacology. 2018;58(6):814-22.

58.   Mashaba TP, Matlala M, Godman B, Meyer JC. Implementation and monitoring of decisions by pharmacy and therapeutics committees in South African public sector hospitals. Expert review of clinical pharmacology. 2019;12(2):159-68.

59.   Sofat R, Cremers S, Ferner RE. Drug and therapeutics committees as guardians of safe and rational medicines use. British journal of clinical pharmacology. 2020;86(1):10-2.

60.   Hoffmann M. The right drug, but from whose perspective? A framework for analysing the structure and activities of drug and therapeutics committees. European journal of clinical pharmacology. 2013;69(Suppl 1):79-87.
*Interesting study documenting key structures and activities for hospital DTCs

61.   Godman B, Malmstrom RE, Diogene E, Gray A, Jayathissa S, Timoney A, et al. Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? Expert review of clinical pharmacology. 2015;8(1):77-94.

62.   Godman B, Malmstrom RE, Diogene E, Jayathissa S, McTaggart S, Cars T, et al. Dabigatran - a continuing exemplar case history demonstrating the need for comprehensive models to optimize the utilization of new drugs. Frontiers in pharmacology. 2014;5:109.

63.   Eriksson I, Wettermark B, Persson M, Edstrom M, Godman B, Lindhe A, et al. The Early Awareness and Alert System in Sweden: History and Current Status. Frontiers in pharmacology. 2017;8:674.

64.   Frisk P, Aggefors K, Cars T, Feltelius N, Loov SA, Wettermark B, et al. Introduction of the second-generation direct-acting antivirals (DAAs) in chronic hepatitis C: a register-based study in Sweden. European journal of clinical pharmacology. 2018;74(7):971-8.

Appendix

ADEs suspected to be caused by remdesivir reported in the WHO database (1004 ADEs from 439 individuals)

Broad Heading	Specific ADEs	Frequency
Blood and Lymphatic System Disorders (N = 20)		
	Anemia	7
	Thrombocytopenia	3
	DIC	3
	Blood Disorder	1
	Coagulopathy	1
	Eosinophilia	1
	Febrile Neutropenia	1
	Leukopenia	1
	Lymphopenia	1
	White blood cell disorder	1
Cardiac Disorders (N = 51)		
	Tachy or Bradyarrythmia	26
	Cardiac and Cardiorespiratory Arrest	17
	Pulseless electrical activity	5
	Cardiac Failure	1
	Coronary Artery Stenosis	1
	Palpitations	1
Ear and Labyrinth Disorders (N=1)		
	Ear hemorrhage	1
Eye Disorder (N = 6)		
	Eye Irritation	1
	Eye Movement Disorder	1
	Eye Pain	1
	Eye Pruritis	1
	Miosis	1
	Ocular Hyperemia	1
Gastrointestinal Disorders (N = 42)		
	Nausea/Vomiting	15
	Diarrhea	10
	GI Hemorrhage	4
	Pancreatitis	3
	Abdominal Pain	2
	Dysphagia	2
	Abdominal Distention	1
	Enteritis	1
	Epigastric Discomfort	1
	Faeces Discoloured	1
	Intestinal Dilation	1
	Intestinal Ischemia	1

General disorders and administration site conditions (N=84)		
	Condition Aggravated/Disease Progression	19
	Death	12
	Multiorgan Disorder/Organ Failure	11
	Pyrexia	11
	Chills	9
	Infusion Site Reaction	8
	Drug Interaction	2
	Fatigue	2
	Malaise	2
	Pain	2
	Discomfort	1
	Disease Complication	1
	Unapproved Indication	1
	Oedema	1
	Hypothermia	1
	Swelling	1
Hepatobiliary Disorders (N = 23)		
	Hepatitis	6
	Hepatic Failure	6
	Hepatic Function Abnormal	2
	Hyperbilirubinaemia	2
	Hypertransaminasaemia	2
	Cholelithiasis	1
	Gallbladder Disorders	1
	Hepatotoxicity	1
	Liver Disorder	1
	Liver Injury	1
Immune System Disorders (N=1)		
	Hypersensitivity	1
Infections and Infestations (N = 36)		
	Sepsis and Septic Shock	18
	Viral Infection	5
	Bacterial Infection	4
	Pneumonia	4
	Fungal Infection	2
	Pyomyositis	1
	Subcutaneous Abscess	1
	Urinary Tract Infection	1
Injury, Poisoning and Procedural Complications (N =73)		
	Medication Error	34
	Product Use in Unapproved Condition	29
	Maternal Exposure During Pregnancy	4
	Accidental Exposure to Product	2

	Inadequate Hemodialysis	1
	Procedural Hypotension	1
	Tracheal Injury	1
	Endotracheal Intubation Complication	1
Investigations (N=283)		
	Hepatic enzyme increased	141
	Blood creatinine increased	49
	Glomerular filtration rate decreased	14
	Abnormal Hemogram	13
	Oxygen saturation decreased	9
	Bacterial test positive	7
	Blood urea increased	4
	Blood electrolyte abnormality	4
	Creatinine renal clearance decreased	3
	Electrocardiogram change	3
	Coagulation tests abnormal	3
	Blood lactic acid increased	2
	Blood pressure increased	2
	Body temperature increased	2
	Heart rate increased	2
	Inflammatory marker increased	2
	Respiratory rate increased	2
	Urine analysis abnormal	2
	Blood albumin decreased	1
	Blood glucose increased	1
	Blood lactate dehydrogenase increased	1
	Blood lactic acid decreased	1
	Blood pressure decreased	1
	Cardiac output decreased	1
	Chest X-ray abnormal	1
	Computerized tomogram abnormal	1
	Fetal heart rate abnormal	1
	Gastric residual increased	1
	Glomerular filtration rate increased	1
	Heart rate decreased	1
	Pancreatic enzymes increased	1
	Protein total increased	1
	Pulse abnormal	1
	Renal function test abnormal	1
	Urine output decreased	1
	Weight decreased	1
	Amylase increased	1
Metabolism and nutrition disorders (N =22)		
	Acidosis	10

	Hyperkaliemia	5
	Fluid overload	2
	Hypokalemia	2
	Decreased appetite	1
	Hypernatremia	1
	Metabolic alkalosis	1
Musculoskeletal and connective tissue disorders (N=5)		
	Hematoma muscle	1
	Muscular weakness	1
	Myalgia	1
	Myopathy	1
	Rhabdomyolysis	1
Nervous system disorders (N = 34)		
	Seizure	4
	Burning sensation	3
	Lethargy	3
	Headache	2
	Tremor	3
	Ischemic stroke	2
	Carotid artery occlusion	1
	Depressed level of consciousness	1
	Disturbance in attention	1
	Dyskinesia	1
	Encephalopathy	1
	Hemorrhage intracranial	1
	Hemiparesis	1
	Hypoesthesia	1
	Hypotonic	1
	Intention tremor	1
	Neuropathy peripheral	1
	Paranesthesia	1
	Paralysis	1
	Psychomotor hyperactivity	1
	Transient ischemic attack	1
	Unresponsive to stimuli	1
	Vertebral artery occlusion	1
Psychiatric disorders (N = 10)		
	Agitation	1
	Anxiety	2
	Confusional state	1
	Hallucination	2
	Insomnia	1
	Intensive care unit delirium	1
	Mental status changes	2
Renal and urinary disorders (N = 102)		

	Renal Injury	63
	Renal impairment	14
	Renal failure	13
	Renal tubular necrosis	3
	Azotemia	2
	Chromaturia	1
	Crystal nephropathy	1
	Dysuria	1
	Hydronephrosis	1
	Nephropathy toxic	1
	Oliguria	1
	Renal ischemia	1
Reproductive system and breast disorders (N = 1)		
	Ovarian vein thrombosis	1
Respiratory, thoracic and mediastinal disorders (N = 89)		
	Respiratory failure	28
	Hypoxia	11
	Acute respiratory distress syndrome	8
	Pulmonary embolism	8
	Dyspnea	7
	Pneumothorax	5
	Respiratory disorder	5
	Respiratory distress	3
	Tachypnea	2
	Throat irritation	2
	Cough	1
	Emphysema	1
	Haemothorax	1
	Interstitial lung disease	1
	Lung consolidation	1
	Lung infiltration	1
	Pneumomediastinum	1
	Pulmonary fibrosis	1
	Pulmonary hemorrhage	1
	Wheezing	1
Skin and subcutaneous tissue disorders (N = 36)		
	Rash	22
	Erythema	4
	Hyperhidrosis	3
	Dermatitis allergic	2
	Blister	1
	Decubitus ulcer	1
	Livedo reticularis	1
	Pruritus	1
	Urticaria	1

Social circumstances (N = 1)		
	Refusal of treatment by relative	1
Surgical and medical procedures (N = 41)		
	Therapy cessation	22
	Dialysis	11
	Hemofiltration	2
	Tracheostomy	2
	Caesarean section	1
	Endotracheal intubation	1
	Renal replacement therapy	1
	Surgery	1
Vascular disorders (N = 43)		
	Hypotension	24
	Shock	9
	Hypertension	4
	Hemodynamic instability	2
	Phlebitis	2
	Thrombophlebitis	1
	Deep vein thrombosis	1