



A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OEB and YN conceptualization of the research project; development of protocol in the manuscript. Authors OEB, YN and JOO research grant of the manuscript. Authors OEB, AAA write up; author YT supervision of data collection protocols in the manuscript. Author OO conceptualization and permits of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i44A36328

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/88971>

Original Research Article

Received 28 April 2022

Accepted 02 July 2022

Published 08 July 2022

ABSTRACT

Aim: To compare outcomes from ivermectin (IVM) - and non-ivermectin (NIVM)-based treatments for COVID-19 in Abuja, Nigeria.

Methods: Sixty-one consecutive virology-proven cases were recruited and managed with IVM-based regimes. A subsequent cohort of 26 patients was treated with NIVM due to physician preference, with varying combinations of lopinavir/ritonavir (Alluvia), remdesivir, azithromycin, and enoxapramin. All patients received zinc sulfate, vitamin C and supportive therapy. Propensity matching was carried out as indicated, and Repeat Measures Analysis of Variance (RMANOVA) allowing for time*treatment interaction was carried out for time dependent variables, deriving Likelihood Ratio (LR) and P values.

Main Outcome Measures: Change in cycle threshold (viral load) over time, positivity status by day 5, improvement in clinical status using myalgia scores, days to discharge (DTD), change in SpO₂ and death.

Results: IVM was associated with a greater and faster reduction in viral clearance (LR=64.2 p< 0.0001 for the N gene): 31% and 95% were negative by days 5 and 14, respectively, versus 0% on NIVM. The mean DTD on IVM was 8.8 days versus 19.4 days, p< 0.0001. IVM proved significantly superior for Myalgia scores, LR= 23.45, P=0.0007. The mortality rate was 0/61 (0%) in IVM but 4/26 (15.3%) in NIVM. Three of the 4 deaths were in females, and 2 had been vaccinated, one fully. The SpO₂ increased significantly more on IVM (p < 0.0001 RMANOVA) than the NIVM group. C-reactive protein and D-dimer levels dropped significantly more sharply during IVM (P= 0.0068, 0.063), suggesting anti-inflammatory and antifibrinolytic activity.

Conclusions: The IVM-based regimen caused earlier discharge from treatment and reduced mortality, in addition to clinical and laboratory improvements. Vaccination did not protect some patients from SARS-CoV-2 breakthrough infection and mortality.

Keywords: SARS-CoV-2; ivermectin; SpO₂%; vaccination; mortality.

1. INTRODUCTION

Following the publication by Caly et al [1] on the efficacy of ivermectin (22,23-dihydroavermectin B_{1a}/B_{1b}) in vitro against SARS Cov2 virus, its role in the management of COVID-19 in vivo has been investigated by several authors [2,3].

The preponderance of evidence, based on various meta-analyses, suggests that the drug is efficacious as prophylaxis and as therapy for COVID-19 [4,5,6]. In Nigeria, Babalola et al [7] demonstrated the superiority of ivermectin (IVM) in viral clearance over alluvia (lopinavir/ritonavir) with a hazard ratio of 2.0 on Cox regression analysis. In addition, Babalola et al [8] compared IVM used alone with the triple therapy of IVM+ hydroxychloroquine (HCQ)+azithromycin (AZM) in Abuja. That study demonstrated that IVM used alone appeared to have sufficient anti-inflammatory and antiviral properties without the need for these adjuncts. As a consequence of these studies and following several anecdotal reports within the country, ivermectin is widely prescribed in Nigeria for COVID-19. However, The lack of official inclusion of ivermectin in the COVID-19 treatment regimen and physician preference has led to disparate prescriptions of ivermectin.

A cohort of patients has thus been treated with a combination of drugs that did not include IVM. These drugs include remdesivir, azithromycin, alluvia and clexane. To compare outcomes, we took the opportunity to apply the same data collection protocol [8] to a non-IVM treated

cohort. This study also provided an opportunity to assess the in vivo antiviral efficacy (if any) of ivermectin, remdesivir, azithromycin, and hydroxychloroquine or various combinations thereof. Furthermore, since vaccinations had been recently introduced in the country, we also had the opportunity to assess the effect of vaccination on symptomatology and mortality in COVID-19 breakthrough patients in Abuja.

The aims of our present study were therefore to evaluate the impact of ivermectin (IVM) and non-ivermectin (NIVM) regimens on viral load, clinical amelioration, days to discharge (DTD) and mortality in patients managed at Abuja Federal Capital Territory (FCT), Nigeria.

2. MATERIALS AND METHODS

Approval to carry out the research was obtained from the University of Abuja Health Research Ethics Committee. The study adhered to the tenets of the Declaration of Helsinki [9].

While the cases for the triple therapy were enrolled between the 20th of April until the 18th of June 2021, the NIVM cases were enrolled between the 20th of September and the 24th of November. From Fig. 1, this would coincide with the second and third waves of the COVID-19 epidemic in Nigeria, specifically towards the tail end of the beta wave (B.1.351 variant) for the IVM series and the tail end of the delta (B.1.617.2 variant) wave for the non-IVM series [10]. However, we did not determine variants in our study population.



Fig. 1. Waves of COVID-19 in Nigeria relative to the collection of cases. First wave-wild type, second-wave Beta third wave-Delta fourth wave-Omicron

Series commenced on approximately 20 April 2021

Ivermectin series.

None Ivermectin series

*Based on WHO COVID 19 dashboard.

Inclusion criteria: Consecutive COVID-19-positive patients of all ages and sexes notified to the Federal Capital Territory COVID-19 Control Center based in Gwagwalada were eligible for inclusion in the trial, provided informed consent was not withheld.

Exclusion criteria: Exclusion criteria were lack of a positive COVID-19 test, refusal to give informed consent, pregnancy, history of heart disease and known or reported allergy to any of the trial medications.

2.1 Study Design

This was a parallel group comparison of ivermectin-based and non-ivermectin-based regimens in COVID-19-positive Nigerian patients. Sixty-one subjects were recruited into the IVM-based comparison study [8], while 26 subjects were subsequently recruited into the NIVM group. The NIVM group received varying combinations of clexane (enoxaparin, a low molecular weight heparin), alluvia (lopinavir/ritonavir), zithromax (azithromycin) and remdesivir (for those who could afford it), but NOT received IVM. Furthermore, all patients in both the IVM and NIVM groups received zinc succinate and vitamin C.

The IVM group was subdivided as follows:

- A. Thirty patients received 200 mcg/kg ivermectin daily for five days. In addition, one patient received Alluvia,

- B. Thirty-one patients received HIA triple therapy

- a. Hydroxychloroquine 200 mg per day for three days
 - b. Ivermectin 200 mcg/kg daily for five days,
 - c. Azithromycin 500 mg per day for three days
- In addition, 2 patients received Alluvia, and 3 received remdesivir.

The NIVM group consisting of 26 patients was treated as follows:

- a) All 26 patients received clexane (enoxaparin) intramuscularly at a dose of 40 i.u. daily throughout admission.
- b) Five patients received Alluvia. 200 mg. bd. for 5-7 days depending on the response.
- c) Four patients received remdesivir. 200 mg stat, then 100 mg daily, for at least six days, maximum 11 days.

Thus, spanning both groups, eight patients received alluvia, while seven patients received remdesivir.

Patients across the board also received the Standard of Care for COVID-19 patients in Nigeria, including zinc sulfate at 50-100 mg daily and vitamin C at 1000 mg daily for 7 days.

Ventilators and Oxygen: A total of ten patients required supplemental high-flow nasal oxygen therapy (HFNOT), 3 in IVM and 7 in NIVM. Three patients required a ventilator, two in the IVM group and one in the NIVM group.

Virology: A GeneXpert machine was used to perform quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Two different RNA particles were measured: N-gene (Nucleocapsid) and E-gene (Envelope). A semiquantitative measure of cycle threshold (Ct) values was derived. Ct is inversely related to viral load. All two marker genes must be negative before a patient was deemed 'negative' for SARS-CoV-2. A Ct of 38 or more is regarded as negative for the E-gene, while a Ct of 40 or more is regarded as negative for the N-gene.

2.2 Parameters Measured

1. Viral Ct was quantified at enrolment (baseline or day 0), day 5, day 14 and day 21 after dosing. The proportion with negative PCR outcomes at days 5, 14 and 21 was assessed for the two groups.
2. SpO₂% was assessed using a pulse oximeter on a daily basis at approximately the same time of the day. Details of the impact of IVM versus NIVM on SPO₂% time course, pharmacodynamics, determinants and correlates are reported in a separate paper.
3. The symptom checklist was assessed at baseline. These included the following:

Respiratory symptoms: Cough.

GIT symptoms: nausea, vomiting, diarrhea, and abdominal pain.

CVS: Tiredness, lassitude, dyspnea

CNS: Headache, Anosmia, Ageusia.

MSS: Myalgia. This was scored using a Likert scale as a sentinel proxy measure for the patient's clinical progress.

The following serious adverse events were monitored: dizziness, diarrhea, vomiting, nausea, appetite loss, stomach pain, tiredness, and others (to be specified).

4. Inflammatory markers were measured at baseline and day 7. These were erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and D-dimer.

5. Haematological variables were measured at baseline and day 7, including haemoglobin, white blood cells, neutrophils, lymphocytes and platelet count. The neutrophil/lymphocyte ratio (NLR) was assessed as a measure of systemic inflammation.

2.3 Statistical Analyses

Data were collected into Android tablets on the JotForm platform and uploaded in real time to the internet cloud, making it accessible by all researchers on the team. The data were ultimately translated into Excel and cleaned. Data were subsequently uploaded into STATA analysis package Stata/IC 16.1 for Mac (Intel 64-bit) and prepared for analysis.

Descriptive and inferential statistics (both parametric and nonparametric where indicated) were performed. Repeated measures analysis of variance (RMANOVA)/Student's t-test and the chi-squared test were performed to assess the effects of treatment on:

1. Change in viral load over time
2. Change in oxygen saturation over time
3. Proportion negative at fixed end points.
4. Changes in the levels of inflammatory markers and hematological variables.
5. Disposition of patients was assessed on a daily basis with regard to whether 1. treatment was maintained, 2. the patient was well enough to be discharged from active care, 3. the patient was referred for further treatment in intensive care, or 4. the patient was deceased.

Statistical rejection of the null hypothesis was $p < 0.05$, and the 95% confidence intervals are quoted.

Propensity matching was carried out where there was a noticeable statistically significant difference at baseline between the IVM and NIVM arms. The initial propensity adjustment was carried out with regard to the baseline SpO₂ value, where the assessment was limited to only cases with SpO₂ <94% at baseline in room air, equivalent to the classification of "Severe COVID-19 diseases" by the National Institute of Health NIH [11].

This propensity matching after adjusting for baseline SpO₂ meant that 21 in the IVM group

and all 26 in the NIVM group were included in the matched analysis.

Furthermore, for the RMANOVA of the change in the rt-PCR cycle threshold over time, the analysis was restricted to cases with Ct values between 20-25 for the N gene and between 14 and 18 at baseline for the E gene.

Univariate analysis was carried out where indicated. Where there is a zero in one of the cells, and 1 is added to all cells to derive approximate odds ratios.

A serious adverse event form was designed and completed for every case enrolled in the trial. A detailed clinical description of such adverse

events was captured and evaluated. Immediate steps were taken to ameliorate such incidents.

Main outcome measures: Change in cycle threshold (viral load) over time, change in positivity status by day 5, improvement in clinical status using myalgia scores, days-to-discharge from care, change in SpO2 over time and death.

3. RESULTS

3.1 Baseline Comparisons

The results describe both unmatched and propensity-matched findings, comparing IVM and NIVM outcomes.

Table 1a. Baseline variables, non-propensity matched comparing IVM- and non-IVM-based therapy

Variable	IVM	NON IVM	Overall	P value (test)
Total Numbers	61	26	87	
Mean Age (SD)years.	40.4	44.8	41.7	0.185(ttest)
Sex (Male %)	39(63.9)	17(65.4)	56(64.4)	0.897(Chi ²)
Oxygen use	3(4.9)	7(29.2)	10(11.8)	0.002
Ventilator	2(3.3)	1(5)	3(3.7)	0.724
Vaccination	0(0)	7(26.9)	7(8.0)	<0.0001
Hematology				
Hemoglobin g/dl	12.8	12.5	12.7	0.603
WBC X10 ⁹ cells/liter	9.5	8.9	9.3	0.242
Lymphocyte X10 ⁹ cells/liter	34.9	45.6	38.1	0.0002(ttest)
Neutrophils X10 ⁹ cells/liter	59.2	57.8	58.8	0.659(ttest)
Neutrophil to Lymphocyte ratio(NLR)	2.27	1.28	1.97	0.023
Platelet count X10 ⁹ cells/liter	199.6	183.2	194.7	0.256
Viral Load Cycle Threshold Ct.				
N-gene CT	26.53	18.25	24.05	<0.0001
E-gene CT	20.96	15.50	19.33	<0.0001
Inflammatory markers				
ESR ml/h Westergren	12.8	12.2	12.6	0.270 (ttest)
C-reactive Protein mg/l	14.7	11.5	13.7	0.0061
D-dimer ng/ml FEU (Fibrinogen equivalent Unit)	222.2	207.5	217.8	0.0025
SpO2%	92.9	87.1	91.1	<0.0001
Symptoms at baseline (%)				
Diarrhea	15(23.7)	2(8)	16(19.05)	0.093
Anosmia	12(20.0)	15(57.69)	27(31.40)	0.001
Ageusia	11(18.03)	8(30.77)	19(21.84)	0.188
Dyspnea	15(25.00)	4(15.38)	19(22.09)	0.324
Headache	30(50.00)	6(23.08)	36(41.86)	0.20
Cough	44(72.13)	7(26.92)	51(58.62)	<0.0001
Myalgia score	1.71	2	1.8	0.018

Table 1b. Propensity matched baseline variables. (SpO2% less than 94%)

Variable	IVM only Group B (%)	NON IVM Group C	Overall	P value (test)
Total Numbers	21	26	47	
Mean Age (SD)years.	39.8	44.8	42.6	0.219 (ttest)
Sex (Male %)	13(61.9)	17(65.4)	30(63.8)	0.805 (chi2)
Oxygen use	2(9.5)	7(29.2)	9(20)	0.100(chi2)
Ventilator	2(9.5)	1(5.0)	3(7.3)	0.578 (chi2)
Vaccination	0(0.0)	7(53.9)	7(31.8)	0.008(chi2)
Hematology				
Hemoglobin g/dl	12.03	12.49	12.30	0.490
WBC X10 ⁹ cells/liter	9.82	8.90	9.31	0.175
Lymphocyte X10 ⁹ cells/liter	32.67	45.65	39.85	0.0010
Neutrophils X10 ⁹ cells/liter	61.14	57.84	59.32	0.422
Neutrophil to Lymphocyte ratio(NLR)	2.90	1.21	2.01	0.0046
Platelet count X10 ⁹ cells/liter	193.7	183.2	187.9	0.534
Viral Load Cycle Threshold Ct.				
N-gene CT	27.33	18.25	22.31	<0.0001
E-gene CT	21.18	15.50	18.03	<0.0001
Inflammatory markers				
ESR ml/h	12.62	12.15	12.36	0.442
Westergren				
C-reactive Protein mg/l	15.13	11.51	13.13	0.010
D-dimer ng/ml FEU (Fibrinogen equivalent Unit)	218.9	207.5	212.6	0.067
SpO2%	89.1	87.1	88.0	0.961
Symptoms at baseline (%)				
Diarrhea	3(15.8)	2(8.0)	5(11.3)	0.420
Anosmia	7(35.0)	15(57.7)	22(47.8)	0.127
Ageusia	5(23.8)	8(30.8)	13(27.7)	0.596
Dyspnea	3(15.0)	4(15.4)	7(15.2)	0.971
Headache	12(60.0)	6(23.1)	18(39.1)	0.011
Cough	17(80.9)	7(26.9)	24(51.1)	<0.0001
Myalgia scores	1.57	2.00	1.80	0.0062

Table 1a compares unmatched baseline data. The two groups were similar in terms of age, sex, use of ventilator, baseline hemoglobin, total white blood cell count, neutrophil count, baseline platelet count, erythrocyte sedimentation rate ESR, symptomatic ageusia, dyspnea and headache.

However, more in the NIVM group required oxygen supplementation, and the baseline lymphocytes were higher, leading to a lower neutrophil-to-lymphocyte ratio.

Table 1b compares baseline values after propensity matching, using only those with SpO2 less than 94%. Twenty-one individuals in

the IVM arm met this criterion, compared with 26 in the NIVM arm. Consequently, differences in baseline values were much reduced. However, the cycle threshold was still significantly different; hence, the values were further restricted for the RMANOVA analysis to Ct less than 18 for the E-gene and Ct less than 25 for the N-gene Rt PCR (Cycle threshold) changes over time in the two arms. (Tables 2a, 2b and Figs. 2a, 2b, 3a, 3b) In the unmatched comparison, 31% were negative by day five in the IVM arm versus 0% in NIVM. In the matched analysis, 28% in IVM were negative by day 5 compared to zero in the NIVM arm (OR 11.8 CI 1.2-551.4, P=0.004).

Table 2a. PCR results (positive/negative) by day in the study by treatment arm (non propensity matched)

Day	Arm	PCR Positive	PCR Negative (Row%)	Total	P value Chi2
Baseline	IVM	61	0(0)	61	NA
	Non IVM	26	0(0)	26	
	Total	81	0(0)	87	
Day 2	IVM	59	1(1.7)	56	0.510
	Non IVM	26	0(0)	24	
	Total	85	1	86	
Day 5	IVM	41	19 (31.7)	60	0.001
	Non IVM	26	0(0)	26	
	Total	63	19	86	
Day 14	IVM	1	59(98.3)	60	<0.0001
	Non IVM	26	0(0)	26	
	Total	27	59	86	
Day 21	IVM	0	60 (100)	60	<0.0001
	Non IVM	10	16(61.4)	26	
	Total	10	76	86	

Table 2b. Rt-PCR results (positive/negative) by day in the study by treatment arm. (Propensity matched)

Day	Arm	PCR Positive	PCR Negative (Row%)	Total	P value Chi2
Baseline	IVM	21	0(0)	21	NA
	NIVM	26	0(0)	26	
	TOT	47	0(0)	47	
Day 2	IVM	21	0(0)	21	NA
	NIVM	26	0(0)	26	
	TOT	47	0(0)	47	
Day 5	IVM	15	6(28.6)	21	0.004 OR 11.8 CI 1.2-551.4
	NIVM	26	0(0)	26	
	TOT	41	6	47	
Day 14	IVM	1	20(95.2)	21	<0.0001
	NIVM	26	0(0)	26	
	TOT	27	20	47	
Day 21	IVM	0	21(100)	21	0.001
	NIVM	10	16(61.5)	26	
	TOT	10	37	47	

Table 3a. Changes in laboratory parameters in both arms of the study over time (non-propensity matched)

Parameter	Baseline	Day 7	Change Baseline-day7. Unless otherwise stated	P value Top: Day7-baseline Bottom: Difference between arms at day7
Inflammatory markers				
ESR (Erythrocyte Sedimentation Rate, mm/hr)				
Study Total	12.6	11.0	1.6	<0.0001
IVM	12.8	11.4	1.4	0.187
Non-IVM	12.2	9.8	2.4	
C-reactive Protein mg/l				
Study total	13.7	5.8	7.9	<0.0001
IVM	14.7	5.6	9.1	0.0068

Parameter	Baseline	Day 7	Change Baseline-day7. Unless otherwise stated	P value Top: Day7-baseline Bottom: Difference between arms at day7
Non-IVM	11.5	6.2	5.3	
D-Dimer FEU				
Study total	217.5	172.5	44.9	<0.0001
IVM	222.2	171.3	50.6	0.0627
Non-IVM	207.8	175.4	32.1	
Hematology				
Hemoglobin				
Study Total	12.8	13.8	-1.2	0.451
IVM	12.8	15.3	-2.5	0.0916
Non-IVM	12.4	10.5	1.9	
WBC				
Study Total	9.3	7.9	1.4	<0.0001
IVM	9.5	7.9	1.6	0.332
Non IVM	8.9	7.9	0.9	
lymphocytes				
Study total	38.1	37.2	0.9	0.433
IVM	34.9	33.5	1.3	0.560
Non IVM	45.6	45.7	-0.1	
Neutrophils				
Study total	58.8	51.9	6.8	0.0001
IVM	59.2	51.9	7.3	0.656
Non IVM	57.8	52.1	5.7	
Neutrophil to Lymphocyte ratio (NLR)				
Study total	1.97	1.93	0.04	0.731
IVM	2.27	2.26	0.01	0.156
Non IVM	1.28	1.16	0.12	
Platelet count X10 ⁹ /liter				
Study total	194.7	148.2	45.9	0.000
IVM	199.6	153.8	45.1	0.874
Non-IVM	183.2	135.4	47.7	
*N-gene Viral Cycle Time (day5-baseline)				
Study total	24.1	35.4	11.3	<0.0001
IVM	26.5	39.0	12.3	0.016
Non IVM	18.2	27.1	8.8	
*E-gene Viral Cycle Time (day5-baseline)				
Study total	19.3	32.2	5.1	<0.0001
IVM	21.0	35.4	14.4	0.0004
Non IVM	15.5	24.8	9.3	
SpO2				
Study total	91.2	94.7	3.09	<0.0001
IVM	92.9	97.7	4.78	0.0039
Non IVM	87.1	89.3	2.23	

Table 3b. Propensity-matched change with time in selected variables

	Baseline	Day 7	Change (Baseline-day 7) Unless otherwise stated	P value Top: Day7-baseline Bottom: Difference between arms at day7
Inflammatory markers				
ESR (Erythrocyte Sedimentation Rate mm/hr.)				
Study Total	12.4	10.6	1.71	<0.0001
IVM	12.6	11.6	0.98	0.045
Non-IVM	12.1	9.8	2.3	

	Baseline	Day 7	Change (Baseline-day 7) Unless otherwise stated	P value Top: Day7-baseline Bottom: Difference between arms at day7
C-reactive Protein mg/l				
Study total	13.1	5.7	7.38	<0.0001
IVM	15.1	5.1	10.01	0.0065
Non-IVM	11.5	6.2	5.27	
D-Dimer FEU				
Study total	212.6	167.7	44.96	<0.0001
IVM	218.9	158.1	60.9	0.046
Non-IVM	207.5	175.4	32.1	
Hematology				
Hemoglobin g/dl				
Study Total	12.3	11.4	0.91	0.0080
IVM	12.0	12.4	-0.38	0.0002
Non-IVM	12.3	10.5	1.95	
WBC				
Study Total	9.31	8.00	1.31	0.0003
IVM	9.82	8.08	1.74	0.287
Non IVM	8.90	7.93	0.96	
lymphocytes				
Study total	39.9	38.7	1.17	0.468
IVM	32.7	29.9	2.76	0.377
Non IVM	45.7	45.8	-0.12	
Neutrophils				
Study total	59.3	52.3	7.09	0.0017
IVM	61.1	52.4	8.76	0.258
Non IVM	57.8	52.1	5.73	
Neutrophil to Lymphocyte ratio (NLR)				
Study total	2.01	1.99	0.02	0.470
IVM	2.90	3.01	-0.11	0.7835
Non IVM	1.28	1.16	0.11	
Platelet count X10 ⁹ /liter				
Study total	187.9	152.6	35.2	0.0006
IVM	193.6	173.9	19.7	0.147
Non-IVM	183.2	135.4	47.8	
*N-gene Viral Cycle Time (day5-baseline)				
Study total	22.3	32.1	9.73	<0.0001
IVM	27.3	38.2	10.85	0.1006
Non IVM	18.2	27.1	8.84	
*E-gene Viral Cycle Time (day5-baseline)				
Study total	18.0	29.7	11.67	<0.0001
IVM	21.2	35.8	14.64	<0.0001
Non IVM	15.5	24.8	9.28	
SpO2				
Study total	88.2	92.6	4.42	<0.0001
IVM	89.1	97	7.42	<0.0001
Non IVM	87.1	89.3	2.23	

Table 4. Some variables on the four individuals who died

Age	Sex	Baseline SpO2	Baseline C-reactive protein mg/l (Normal<10)	Baseline N-gene Cycle threshold	Vaccinated	Remdesivir use	IVM	Concurrent illness
35	F	88	11.6	16.2	yes	yes	no	Nil of note
63	F	81	12.2	17.1	.	no	no	Nil of note
36	F	88	10.2	20.6	Yes (2 doses)	yes	no	Peptic ulcer Disease
25	M	88	12.5	16.1	no	yes	no	Nil of note

Table 5. Ranked antiviral effect of various combinations of drugs as seen in the study, based on change in cycle threshold between baseline and day five

Serial	Drug/intervention	n	Mean change in Cycle threshold Day5-baseline	Difference (drug-no drug)	P value (ttest or as stated) Comments
1.	IVM+REM	3	19.1	8.10	0.0313 Wilcoxon Rank sum test
	NIVM+REM	84	10.9		
2	Any IVM	60	12.33	3.48	0.0058 IVM singly or in combination.
	NIVM	26	8.84		
3	IVM alone	19	11.95	3.11	0.0181
	NIVM	26	8.84		
4	*HIA therapy	35	12.78	2.53	0.026 HCQ, IVM, AZT
	Non HIA therapy	51	10.25		
5	Any Remdesivir	7	13.46	2.37	0.314 Remdesivir singly or in combination
	Non-Remdesivir	79	11.08		
6	Alluvia	8	12.56	1.41	0.523 Lopinavir+Ritonavir
	Non-Alluvia	78	11.14		
7	Azithromycin	61	11.10	-0.60	0.672
	Non-Azithromycin	25	11.70		
8	Vaccinated	7	7.55	-3.38	0.084
	Not vaccinated	33	10.94		

Note: When remdesivir is used alone, the mean change from baseline to day 5 is only 9.25
*HIA: hydroxychloroquine+ivermectin+azithromycin

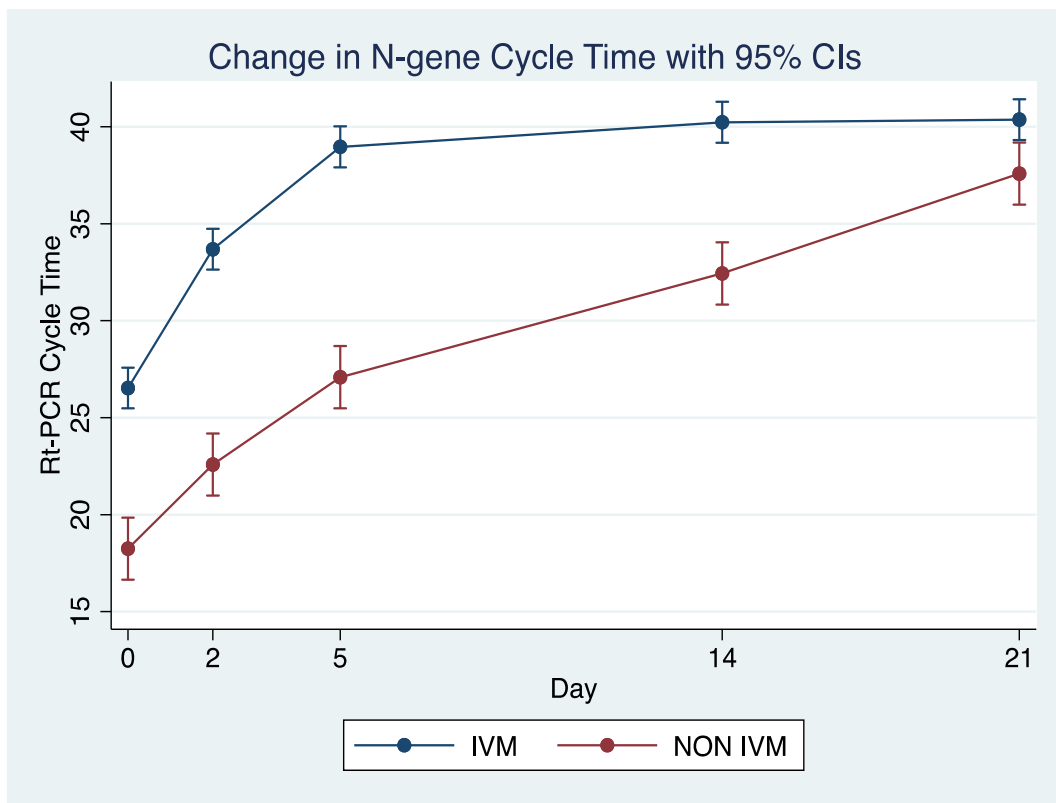


Fig. 2a. Change in the N-Gene Rt-PCR cycle threshold over time, unmatched

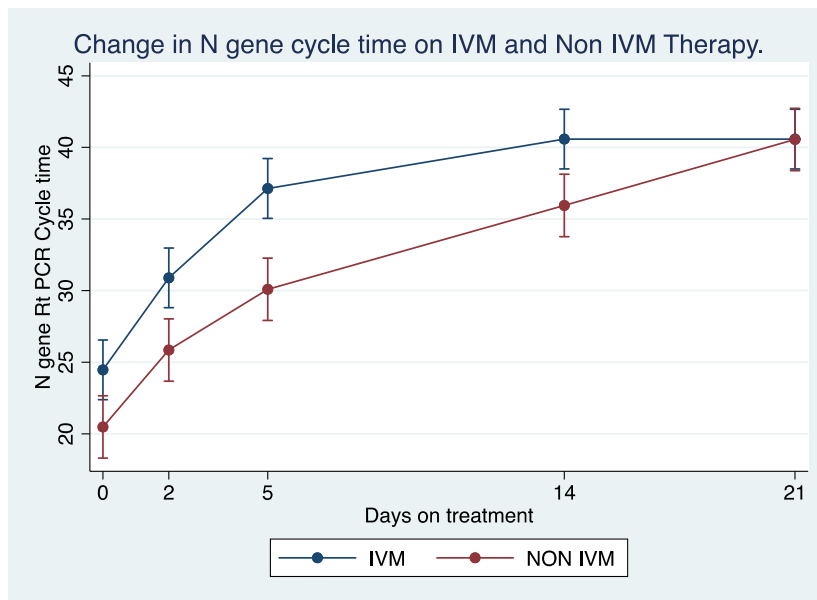


Fig. 2b. Change in N-Gen Rt-PCR Cycle threshold over time, Propensity matched (Baseline between 20-25). Note that by day 5, most patients on IVM are already in the 35-40 bracket as opposed to the non-IVM group. P<0.0001

Table 6. The effect of vaccination on symptoms at baseline in the study

Symptom	Vaccinated No (%)	Unvaccinated No (%)	P value	Odds Ratio
fever	2(29)	21(64)	0.088	4.4
headache	2(29)	17(52)	0.270	2.7
cough	2(29)	22(65)	0.077	4.6
dyspnea	0(0)	8(24)	0.145	NA
diarrhea	0(0)	5(16)	0.254	NA
*Myalgia scores	1.86	1.84	0.971	NA
Increase in myalgia scores by day 7	2.00	2.19	0.669	NA

*Myalgia scores are based on a Likert scale. The lower the score, the worse the myalgia

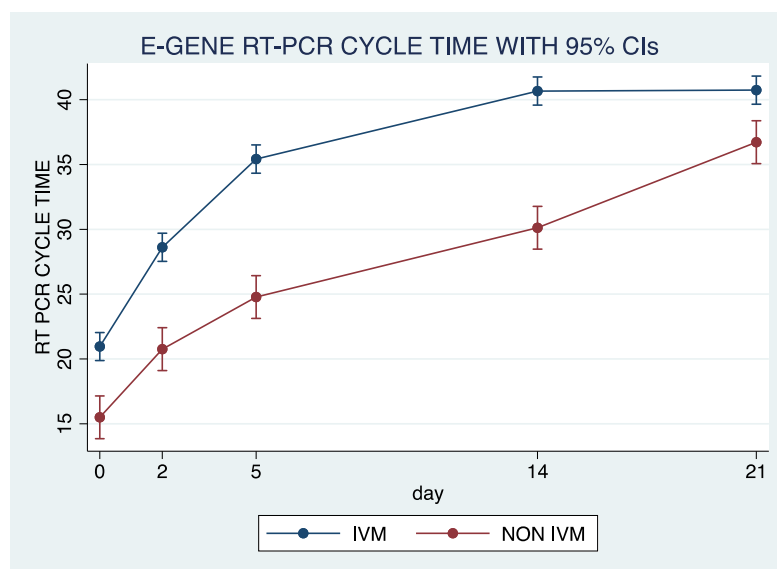


Fig. 3a. Change in E-gene Rt-PCR cycle threshold Ct over time, unmatched

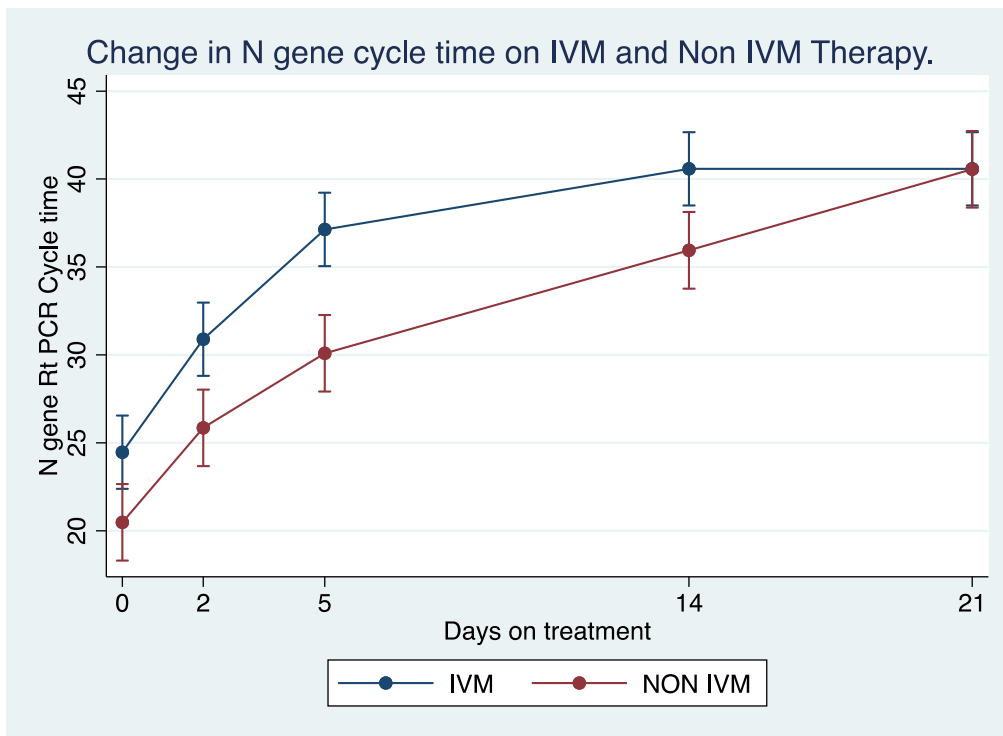


Fig. 3b. Change in N-Gene Rt-PCR Cycle threshold over time, Propensity matched (Baseline between 20-25)
 Note that by day 5, most patients on IVM are already in the 35-40 bracket as opposed to the non-IVM group.
 $P < 0.0001$

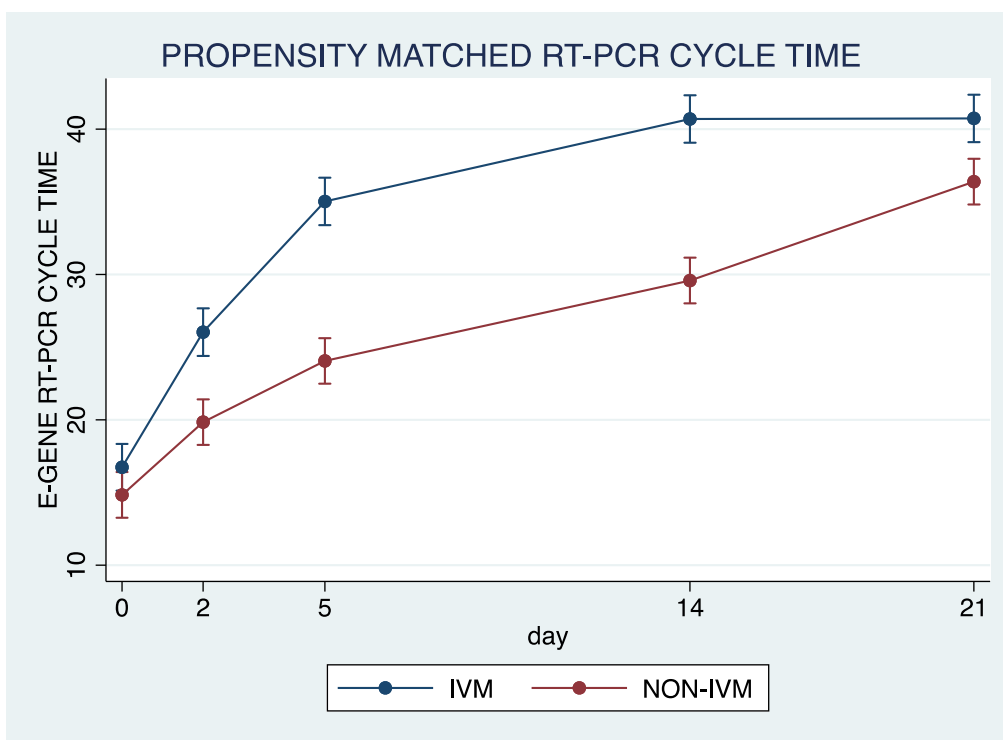


Fig. 3c. Change in E-gene Rt-PCR cycle threshold Ct over time (baseline between 12-16)
 Note that by day 5, most patients on IVM are already in the 35-40 bracket as opposed to the non-IVM group.
 $P < 0.0001$

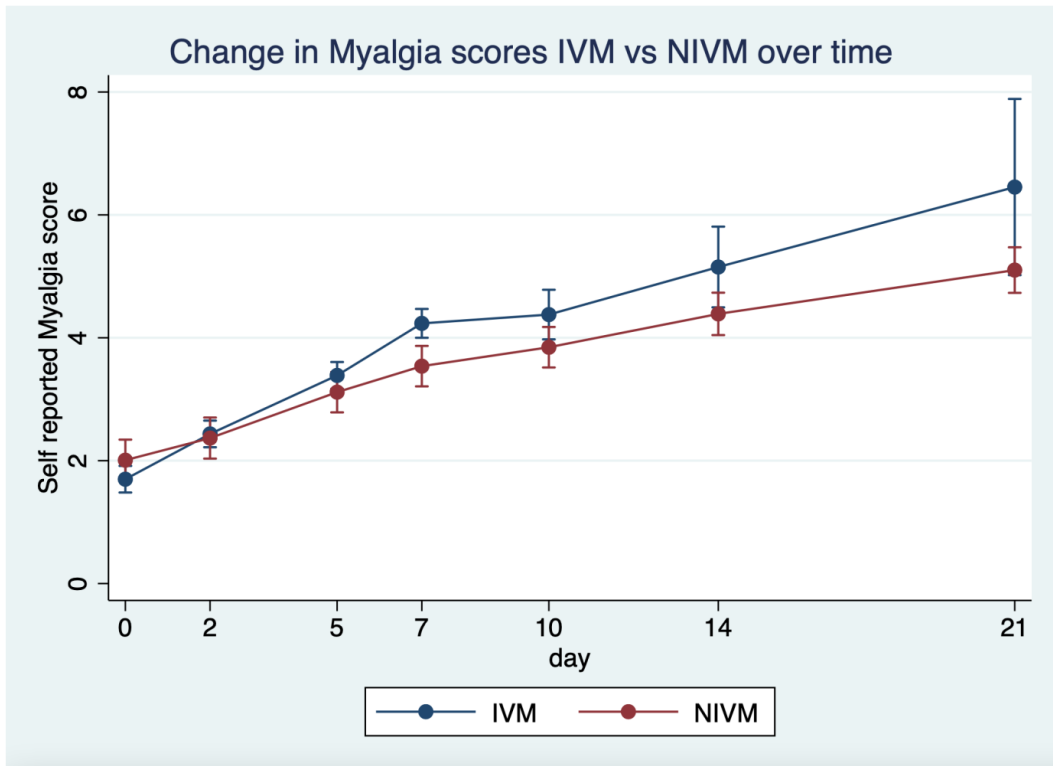


Fig. 4. Change in Myalgia scores over time IVM versus NIVM. (Note: Unmatched data used because the baseline scores were closer in this instance) Likelihood ratio 23.45, P=0.0007

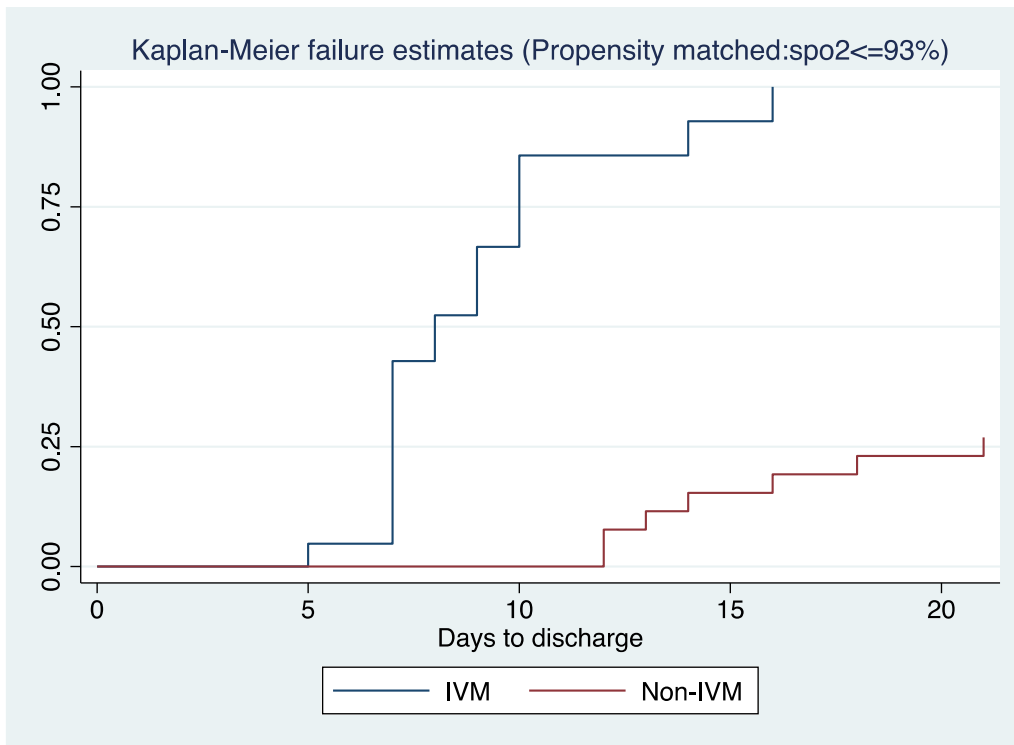


Fig. 5. Kaplan-Meier curve showing Days-to-Discharge (DTD) from care for the IVM and NIVM groups in Abuja hospitals. Mean DTD for IVM=8.8, for NIVM=19.4., P<0.0001 (Propensity matched)

By day 14, the proportion of negative cases rose to 95.2% in IVM versus non-negative cases in NIVM. By day 21, all IVM was negative versus 61.5% negative in NIVM.

RMANOVA showed significant differences between the IVM and NIVM arms (both for models assuming no time interaction and models assuming treatment*time interaction), meaning that ivermectin-based therapy resulted in much more efficient viral clearance than non-ivermectin-based therapy for COVID-19.

LR=41.7 $P < 0.0001$ for change in Ct E-gene over time and LR=64.2, $P = 0.0000$. For N-gene in the treatment*time interaction models.

Figs. 2a and 2b and 3a and 3b show matched and unmatched time sequences for the N gene and E gene, respectively, indicating that by day 5, a significant proportion of patients in the IVM arm were already in the negative zone, in contrast with patients in the NIVM group.

Changes in SpO2 over time: The SpO2% increased significantly more on IVM ($p < 0.0001$ RMANOVA) than the NIVM group. The time course of the changes and the predictors and correlates of the increase in SpO2 using IVM-based treatment are reported in a separate paper.

Changes in Inflammatory markers: (Tables 3a and 3b) Changes in the erythrocyte sedimentation rate (ESR), C-reactive proteins and D-dimer levels between baseline and day 7 were assessed in both arms and for matched and unmatched data. There was a significant drop in these markers in both arms of the study. However, CRP and D-dimer levels dropped at a significantly faster rate in the IVM arm. ($P = 0.0068$ and 0.063 , respectively), suggesting significant anti-inflammatory and antifibrinolytic activity of IVM.

Changes in hematological variables: There was a net increase in hemoglobin levels in the IVM arm of the study compared to a net decrease in the NIVM arm, and this difference was statistically significant in the matched data ($P = 0.0002$).

There was a decrease in white blood cell count across the board without a statistically significant difference in the two arms. However, there was a slight increase in lymphocyte count in the NIVM

arm, which reflected a lower neutrophil to lymphocyte ratio. This difference was not statistically significant.

Changes in clinical status: The mean increase in myalgia scores by day 7 was 2.43 in the IVM group versus 1.52 in the NIVM group, $P = 0.0001$. In RMANOVA modeling allowing for a time*treatment interaction, IVM proved significantly superior, likelihood ratio = 23.45 $P = 0.0007$. This suggests that, clinically, the IVM group improved much faster than the NIVM group. (Fig. 4)

Mortality: Of 61 patients in the IVM arm, none died. However, there were four (15.3%) deaths in the NIVM arm, $P = 0.002$, χ^2 . A closer look was taken at the four patients who died in Table 4. Three were female, all had baseline SpO2 < 90%, all had baseline CRP > 10, all had baseline N-gene Ct less than 21, two of them had received vaccination (presumably Astra Zeneca, one double vaccinated) and three of them had received remdesivir in addition to other treatment. One of the patients had peptic ulcer disease (PUD), while the others had no significant concurrent illness.

Influence of various drugs and combinations on outcome (Table 5). We attempted to assess the antiviral efficacy of the various medications used in this study by comparing the increase in cycle threshold Ct by day 5 of 'treatment with' and 'treatment without' the drug, singly or in combination. The results are shown in table 5, where the outcomes are ranked from most effective to least effective. It would appear that the best combination in this series was ivermectin plus remdesivir, which increased the Ct by 19.1 relative to 10.9 without it. This was followed by any IVM combination, IVM alone, HIA therapy, remdesivir singly or in combination, and Alluvia. Azithromycin was associated with a decrease in Ct values, as was a vaccinated status.

Influence of vaccination (Table 6): Although COVID-19 vaccination was introduced in Nigeria in March 2021, uptake has been very low, and as of February 2022, only 7.2% had had at least one dose of vaccine, while only 2.6% were fully vaccinated. Information on vaccination status was obtained from 41 individuals in the study. Only seven individuals had taken at least one dose. The vaccines available in Nigeria are the Astra-Zeneca vaccine and the Moderna vaccine [12].

In the study, there was a reduction in the incidence of fever, headache, cough, dyspnea and diarrhea in the vaccinated group, but none achieved statistical significance. There was no difference in myalgia scores between the two groups. However, two people died who had been vaccinated. OR 13.2 95% CI 0.531-801, P=0.017.

Finally, days to discharge from care (DTD) were assessed for both groups. Fig. 5 is a Kaplan-Meier curve showing DTD for the IVM and NIVM groups in Abuja hospitals. This demonstrates clearly that patients on IVM-based therapy tended to be discharged much earlier. Mean DTD for IVM=8.8, for NIVM=19.4. P<0.0001. This was based on propensity matched data.

4. DISCUSSION

This paper sets out to compare the efficacy of IVM-based care with NIVM in the city of Abuja. As indicated earlier, although ivermectin is widely used in Nigeria, there is no Federal mandate for its use in the care of COVID-19 patients; hence, there is still room for physician preference. Complicating the analysis is the fact that data were collected at different time points in the epidemic, with the inevitable shifting of dominant variants. While the dominant strain during the collection of the IVM data was B.1.351, it shifted to B.1.617.2 during the collection of the NIVM series. This may account for the differences in

the baseline data, particularly concerning SpO₂% and viral cycle threshold Ct. This led to the necessity to carry out propensity matching in this analysis. Our references to the results in this discussion will concern the propensity matched analysis unless otherwise stated.

Some dichotomies are inescapable in the outcome from both arms. Ct RMANOVA analysis clearly indicated the superiority of IVM-based therapy, such that approximately 30% of the patients were in the negative zone by day 5 compared to none in the NIVM arm. The antiviral properties of ivermectin to a host of viruses, including HIV 1, dengue fever, yellow fever virus, and Japanese encephalitis, among others, were known even before the COVID-19 outbreak and alluded to by Satoshi et al as far back as 2014 [13].

In addition, Caly et al [1] demonstrated its use against SARS-CoV-2 in monkey kidney cells. Initial anxieties that the therapeutic doses may not be achieved have been allayed by the fact that IVM selectively concentrates in lung cells where therapeutic levels can be attained [14]. Consequently, several authors have demonstrated the in vivo antiviral efficacy of IVM [7,15,16,17,18]. This has been further confirmed with our study.

The mechanism of action of IVM as a COVID-19 antiviral has been considered by several authors. These include the following:

Serial	Mechanism (Reference(s))
1	It binds to the spike protein of the virus and binds to the ACE2 receptor of the host cell [19]
2	IVM binds to the IMP α component of the IMP α/β 1 heterodimer and thereby blocks the nuclear transport of viral proteins [20].
3	IVM prevents viral protein assembly <i>in vitro</i> [21]
4	It selectively accumulates in the lungs over 10 times higher than predicted [22].
5	IVM promotes the expression of several IFN-related genes (i.e. Interferon-related genes), such as IFIT1, IFIT2, IFI144, ISG20, IRF9, and OASL [23].
6	IVM inhibits lipopolysaccharide (LPS)-induced production of inflammatory cytokines by blocking the NF- κ B pathway and improving LPS-induced survival in mice [24].
7	IVM acts on the JAK-STAT pathway, PAI-1 and COVID-19 sequelae.
8	It inhibits STAT-3- and SARS-CoV-2-mediated inhibition of IFN and STAT 1, with the subsequent shift to a STAT 3-dominant signaling network that could result in almost all of the clinical features of COVID-19; STAT-3 acts as a "central hub" that mediates the detrimental COVID-19 cascade [25].
9	IVM blocks activation of the NF-kappa B pathway and inhibition of toll-like receptor 4 (TLR4) signaling [26].
10	IVM suppresses immune cell recruitment, cytokine production, IgE, and IgG1 production and mucus hypersecretion by goblet cells [27].
11	Ivermectin has been shown to increase prothrombin time by disrupting vitamin K-dependent clotting factors II, V, VII, and X [28,29].

It is clear that, as Wagstaff et al suggested [14], the broad spectrum activity of ivermectin is because it acts, among its several other mechanisms, as a host-directed agent (HDA).

The apparent synergistic effect of ivermectin when combined with remdesivir is also worth noting. From our findings, ivermectin appears to be a more potent anti-SARS-CoV-2 agent than remdesivir, but when the two drugs were combined in 3 of our patients, a rapid increase in cycle threshold was observed. This number is few, so caution has to be observed. (Table 5).

Using *in silico* experiments, Bobrowski et al [29] al. al. alluded to the possible synergistic and antagonistic effects of drug combinations for COVID-19. They suggested that HCQ is antagonistic to remdesivir but synergistic with nitazoxanide. Unfortunately, they did not include ivermectin in the model. Hashem MK [30] of Assiut University registered a trial of ivermectin + remdesivir in the management of COVID-19, but it is not clear whether the trial was carried out or the results were published. It would therefore appear that ours would be the first report on this possible synergistic effect.

Triple therapy with HCQ, IVM and AZT appears less effective in viral clearance. As seen in table 5, AZT appears to lead to a drop in Ct by day 5, suggesting that it may have antagonistic properties to IVM and/or HCQ. The Alluvia effect appears to be very weak in our hands. This is buttressed by the finding of Babalola et al [7] that, when compared to IVM, Alluvia is much less effective in viral clearance. Unexpectedly, vaccination status appears to have a negative effect on early viral clearance in this study.

Ivermectin has been associated with an increase in SpO₂ [31] in contrast to an initial decrease in SpO₂ with NIVM therapy over the first four days of treatment. The same has been borne out by our findings. Details of changes in SpO₂ are discussed in a sister publication.

IVM is associated with a more significant lowering of inflammatory markers, such as C-reactive protein and D-dimer, than NIVM. The effect on ESR was, however, comparable in both groups. The anti-inflammatory effects of ivermectin are not restricted to lipopolysaccharide (LPS) or toll-like receptor 4 (TLR4) signaling but also involve suppressed activation of both NF-kappaB and the stress-activated MAP kinases JNK and p38 [32]. It will

be noted that in the late stages of severe COVID-19, the cause of morbidity and death is not necessarily the viral load but the runaway cytokine storm with consequent respiratory distress.

The anti-inflammatory properties of ivermectin may contribute to the protection from mortality that we observed in this study. (0 out of 61 in the IVM arm versus 4 out of 26 in the NIVM arm.). This protection from mortality has been reported by several workers [33,34].

In addition, there was a more rapid clinical improvement in IVM and a significantly earlier discharge from care, in line with other workers who have found the same [35].

Only seven members of this cohort had received at least one dose of vaccination, a reflection of the low vaccination rollout in Nigeria. There is much skepticism about vaccination, which is fueled by misinformation and disinformation. The fact that there is still a substantial amount of breakthrough infection, as we saw in this cohort, can in fact discourage people from getting vaccinated. Ironically, in this series, there seemed to be a higher likelihood of infection and death in the vaccinated, contrary to the received wisdom. However, vaccinated patients developed fewer symptoms in general, as other authors have noted [36].

Patients with COVID-19 are at high risk of developing a venous thromboembolism (VTE), and it is essential that effective thromboprophylaxis with parenteral drugs (such as Low Molecular Weight Heparin LMWH) drugs such as Clexane aka enoxapramin) be considered for all patients admitted to the hospital, especially in cases of severe pneumonia. In this study, Clexane was given to all NIVM patients but not to the IVM patients. This caused a more but not significantly different reduction in platelet count in NIVM relative to IVM (P=0.156), suggesting that by itself, IVM had comparable platelet reduction capabilities. Caution should thus be exercised in combining LMWH drugs with IVM.

5. CONCLUSIONS

After propensity matching for baseline SpO₂ and viral loads, IVM-based therapy shows significant superiority to NIVM-based therapy in Abuja patients managed for COVID-19 in terms of increase in SpO₂, reduction in viral load,

reduction in days to discharge, earlier improvement in clinical morbidity, and reduced mortality. It is recommended that IVM be included in the treatment of patients with COVID-19.

6. STUDY LIMITATIONS

This is not a randomized trial; actual viral phenotypes were not assessed, and cytokines were not measured.

DISCLAIMER

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ETHICS APPROVAL AND CONSENT

The Project was approved by the University of Abja Teaching Hospital Human Research Ethics Committee. The Approval number was UATH/HREC/PR/2020/015/10. Consent to participate was obtained from each individual patient using a standard consent form in which the project was explained.

ACKNOWLEDGEMENTS

Tobi Babalola for work on the data collection platform.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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