[Appendix 1] Subject Information Sheet and Informed Consent Form

Subject Information Sheet

Study Title:	**High-Dose Vitamin D3 in the Treatment of Human Immune Deficiency Virus Patients, A Double-Blind Randomized Control Trial.**
Institution Name/Investigator Name:	**Hospital / ▣▣ Fatima Majeed**
IRB Number:	**238**
Subject Identification Code (Screening Number):	**▣▣ S [ ][ ]**

You have been invited to take part in this study by the study doctor. However, before you make a decision to participate in this study, it is important to understand accurately why this study is conducted, what will be done, and how it will be done. This information sheet has been prepared to explain the purpose of this study and the overall information such as procedures performed when you participate in this study and the duration. Please take your time to read this sheet carefully. If you have any questions, you may ask the study doctor or study staff. There may be words in the information sheet that are difficult to understand, but the study doctor or study staff will explain words or information that you do not understand upon your request. Taking part in this study will be decided voluntarily. If you agree to participate in the study, you will sign an attached informed consent form, and receive this subject information sheet and a copy of the singed informed consent form.if the subject information sheet and signed original informed consent form that you provided need to be destroyed, the original informed consent form signed by you and your study doctor will be replaced with a photo, and the subject information sheet will be provided to you again when you are released from quarantine.

Participation in this study is voluntary, therefore, you, the subject, may choose to participate out of your free will. The subject's willingness is most important, and even if you do not give consent for participation after receiving an explanation about the study, you will not have any problem, so please take time to consider before making a decision about participation.

1. Study Background and Objective

This study will be conducted for research purposes. Research means that the efficacy and safety of the study drug have not been fully validated at this time.
Human immunodeficiency virus (HIV) is a key challenge for global health. Vitamin D deficiency is common in people living with HIV infection. Antiretroviral therapy (ART) may create unique risk factors for vitamin D insufficiency, including alterations of vitamin D metabolism by ART. Vitamin D supplementation in HIV-infected patients have not previously been investigated in Pakistan and it is unknown whether sufficient physiological levels is

associated with improved clinical outcome or not. We have designed this study with the hypothesis, that the addition of high dose of vitamin D supplementation would be effective in elevating serum 25-hydroxy vitamin D concentration into normal physiological range in patients with HIV infection and this would improve their clinical outcome over the period of 6 months' treatment. The primary outcome of the study will be the sufficient elevating level of serum 25-hydroxyvitamin D at 24weeks. Secondary outcome of the study will be, the increase means CD4 count, decrease in viral load and improvement in liver function test and to reduce the severity of clinical symptoms.

2. Study Procedures and Precautions

Once you have voluntarily provided written consent to participate in the study, a screening test will be conducted to determine your eligibility to participate in the study, and you will be able to participate in the study only if you are considered eligible according to the inclusion/exclusion criteria.

The investigational products consist of 1000,00 (test drug) or placebo (dummy drug, control drug). In order to obtain more accurate study results, this study is designed in a way that both you and the study doctor will not know which drug you will receive while you participate in this study.
You have a 50% chance of receiving 1000,00IU (test drug) or placebo (dummy drug, control drug).

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The detailed study schedule is as follows, and the clinical procedures will be performed by the study staff .

	Screening	**Treatments**			
	V 1 **Screening &** **Assessment**	**V 2** **Randomization** **& 1st Dose**	**V 3** **2nd** **dose**	**V 4** **3rd dose**	**V 5** **Post** **Assesments**
	-7~1	**1 Day**	**5 week**	**12 week**	**24 week**
ICF	×				

Eligibility Criteria	×	×			
Baseline Questionnaire	×				
Weight	×		×	×	×
Height	×		×	×	×
Vital Signs	×	×	×	×	×
Vit-D	×			× V4+1 Day	
CD4 count	×			× V4+1 Day	
Viral load	×			× V4+1 Day	
PCR	×			× V4+1 Day	
CBC	×			× V4+1 Day	
Study Medication		×	×	×	
AE Monitoring		×	×	×	×
RDA					×
End of Study					×

If you decide to participate in this study and sign the informed consent form, the following

Benefits Expected from Study Participation

If you participate in this study, you may expect a treatment effect; The effect and safety information of vitamin-D obtained from this study may be used as supporting data for the treatment policy of HIV patients with vitamin-D deficiency and may contribute to the national health.

3. Expected Precautions for Use of Investigational Products

All drugs may cause side effects (adverse events) in some cases, and the possibility of new side effects (adverse events) that are unknown so far cannot be ruled out. Any new information related to the safety, etc. obtained while conducting the clinical study will be provided to subjects or their legally acceptable representatives in a timely manner. Our treatment is vitamin-D which is mainly a vitamin and provide positive effects with ART. It would be not harmful like other drugs because every human body need this vitamin as pro-hormone and it is helpful in immune-modulatory mechanism of white blood cells, which provide us immunity.

4. Other Treatments

There is no standard option for treatment of hypovitaminosis-D3 in HIV patients on ART.

Consent to Participate in the Study and Withdrawal of Consent

Participation in this study is voluntary, therefore, you, the subject, may choose to participate out of your free will. Even if you do not give consent to participate after receiving an explanation about the study, it will not be a problem. Also, consent for participating in the study can be withdrawn at any time during this study period if the subject wishes, and it is guaranteed that there will be no disadvantages in the future due to the consequent discontinuation of the study.

If any new information which may affect your willingness to continue participation in the study becomes available, the study doctor will inform you as soon as possible. You can use this information to decide again if you would like to continue your participation in the study.

5. Measures for Compensation and Treatment for Damages

Researcher or principal investigator.will be financially responsible for the side effects (adverse events) related to this study, including appropriate treatment, in accordance with the "participant compensation rule", considering the degree, persistence, etc. of the side effects (adverse events). Therefore, we will take appropriate measures as soon as possible if you tell the study doctor at any time if any side effect (adverse event) occurs.

6. Compliance Requirements for Subjects

You must comply with the following for your protection during the study participation and for the accuracy of the study.

a. Please adhere to the visit schedule.
b. If a side effect (adverse event, or undesirable symptom, sign or disease that newly develops after drug administration) occurs, please contact your study doctor immediately and follow your study doctor's instructions. If additional tests are required, you have to visit the hospital for such tests.
c. If drugs other than the drug prescribed by the study doctor during the study is used after administration of the investigational product, or the following prohibited concomitant medication is inevitably administered during the study treatment period, you should notify the study doctor and study nurse of the treatment and the reason for the treatment.

- Other investigational agents
- Drugs that are known to possibly affect the progress of treatment for deficiency of vitamin-D3

7. Confidentiality of Personal Information/Medical Data of the Subjects

Records that can identify you will be kept confidential and will not be publicly accessible. However, the monitor, the auditor, the Institutional Review Board (IRB), the subject protection center, and government agencies may directly access your medical records and data to verify the reliability of study procedures and data within the scope permitted by applicable laws and regulations, but even in this case, confidentiality will be maintained as much as possible. No data will be identified by name, and even if the study results are published, the data will be coded, and your identity will be protected. Collected information will be used for 3 years from the date of study imitation and the date of study completion and will be appropriately managed under the Personal Information Protection Act.

8. Expected Duration of Study Participation

Your participation in this study is planned to last up to approximately 4 weeks (screening period of up to 1 day, treatment period of up to 2 weeks, safety follow up period of up to 2 weeks). However, the verification process for the test results may be delayed, and the duration of participation may be delayed or shortened somewhat from the planned duration of participation due to the occurrence of side effects (adverse events) or the course of treatment during the study.

9. The Number of Subjects Involved in the Study

A total of approximately 95 HIV patients who have been exposed to vitamin-D deficiency on ART will participate in this study.

10. Expenses and Monetary Compensation

If you participate in this study, you will be provided with the investigational product used in this study. In addition, researcher will pay for all test fees such as vitamin-D test conducted as per the protocol. However, you will be responsible for the cost of hospitalization, medical examination, or drugs irrelevant to this study.
If outpatient visits are required, you will be paid 300 PKR for the regular visits to cover your study participation costs (Visit 1:PKR 300, Visit 2:PKR 300, Visit 3 PKR 300, Visit 4: PKR 300), and for unscheduled visits, you will be paid PKR 500 per visit to cover your travel costs. Even if you are withdrawn during the study, travel expense will be provided for the number of visits you make, and the amount is subject to change depending on the extent and duration of study participation.

11. Circumstances under Which the Subject's Participation in the Study May Be Terminated

If any condition(s) observed during the study is determined to be unacceptable to continue the study, the study doctor or the sponsor may stop your participation. In addition, the study may be discontinued upon the decision of the IRB to stop.
Other reasons to stop your study participation may include:

1) It is found during the study that you have been enrolled in the study despite your ineligibility (It is later found that you were not eligible from the screening tests)
2) You have difficulty in continuing the study due to a side effect
3) You or your legally acceptable representative requests withdrawal from the study
4) Subject does not agree with or follow the instructions of the study doctor concerning the investigational product
5) You are lost to follow-up
6) You have difficulty in continuing the study as assessed by the study doctor

If you are withdrawn from the study for any of the above reasons, you will need to go through the procedures scheduled for the last visit (12th week) of the study treatment period. Your data collected up to withdrawal from the study may be used later in the analysis and reporting of the study result. All data collected will be treated anonymously, and any record that identifies you will be kept confidential.
Additional data collected after withdrawal from the study for safety reasons may be used for reporting to the vitamin-D deficiency in HIV patients.
Even after discontinuation of your participation in the study, your study doctor will provide appropriate treatments to improve your symptoms. In addition, if you discontinue participating in the study due to a side effect (adverse event), etc. during the study, the study doctor will provide appropriate treatments and follow-up to check the course of the adverse event until it resolves.

12. Confidentiality of Personal Information

Your information collected in association with this study will be protected by relevant laws

such as the Personal Information Protection Act. Therefore, your study doctor would like to explain to you personal information (including sensitive information) collected during the study, purpose, retention period, use, provision, etc. and receive consent. In addition, all data collected from you will be treated anonymously, and any record that identifies you will be kept confidential. However, if there is a request from the sponsor to publish the study results, your data may be used both domestically and internationally. Your identity will be kept confidential even if the study results are published.

The purpose of collecting and using your personal information and sensitive information is to utilize them in this study and to organize, analyze and report the results.

Your personal information and sensitive information that are collected for this are as follows:

Information type	**Item**
Personal information	Name (including initials), age (month and year of birth), gender, address/telephone number, account number, etc.
Sensitive information	Medical records (medical history, prior medications, use of contraception, pregnancy status, test results, etc.)

Your personal and sensitive information as described above may be retained and utilized for up to 3 years (from the date of study completion or approval) within the scope of the study purposes.

Your personal information collected during your study participation, your medical records observed by the study doctor, sensitive information such as health related information, etc. will be provided to the study sponsor, **The study data provided as above will be sent along with the subject identification code with your name, address, or any item that directly identifies you removed.** In addition, the study data may be provided to the **IRB**, either alone or in conjunction with other study data, within the scope required by applicable laws.
The study researcher, IRB, clinical trial.gov may directly access your data during or after the study to validate the study procedures and data reliability. If you sign this consent form, you agree to permit direct access to your medical records by the monitor, the auditor, the IRB, and the Minister of Food and Drug Safety without violating your confidentiality, to the extent permitted by the applicable laws and regulations. Of course, these data will be utilized by those listed above solely for the purpose of carrying out their obligations related to this study.

You may refuse collection and utilization of your personal information and sensitive information, and may refuse to provide the information to third parties, such as an organization delegated to a specific part of the study, and the IRB. **If you do not consent to the collection and utilization of personal information and the provision of the information to third parties, you will not be able to participate in this study, but there will be no other disadvantages.**

13. Contact for Emergency

Your information collected in association with this study will be protected by relevant laws such as the Personal Information Protection Act. If you want to know more about the personal information (including sensitive information) collected during the study, purpose, retention period, this study or if you need to contact us for medical purposes, you may contact the study doctor and study staff at any time:

Study Doctor:
Contact:
24-hour Contact Number:

Study Staff:
Contact:

If you have any questions concerning the rights of subjects, please contact:

Institutional Review Board of ▣▣ Hospital
Contact:

If you have read this information sheet and agree to participate in the study, please date and sign the informed consent form. The informed consent form has been approved in writing by the IRB.

Informed Consent Form

1. I have been carefully informed of, from the study doctor, have had the opportunity to ask questions and fully understood all of the information regarding this study and the collection and utilization of personal information (including sensitive information).
2. I understand that I am free to make my decision about my participation in the study and the collection and utilization of personal information (including sensitive information), and have the right to refuse this at any time during my study participation and that there will be no disadvantages to me.
3. I understand that I can ask questions about the study at any time, if I have any.
4. I understand that, only for the study purposes, direct access to my medical records, the collection, processing, and utilization of my information, and the provision of the information required to third parties will be permitted.
5. I understand that I will receive a copy of each of the subject information sheet and the informed consent form.

☐ **I understand and agree with the collection and utilization of personal information, and the provision of the information to third parties.**

☐ **I understand and agree with the collection and utilization of sensitive information, and the provision of the information to third parties.**

☐ **I agree to participate in this study voluntarily.**

Subject	Name:	_____	(Signature)	DD MMM YYYY
Legally Acceptable Representative*	Name:	_____	(Signature)	DD MMM YYYY
	Relationsh p to Subject:	_____		
Witness**	Name:	_____	(Signature)	DD MMM YYYY
Investigator***	Name:	_____	(Signature)	DD MMM YYYY

*Legally acceptable representative of the subject if the subject is incapable of making decisions about participation (If there is no legally acceptable representative, a representative is appointed in the order of spouse, immediate family, and non-immediate family; if there are more than one immediate or non-immediate family members, it should be decided under agreement. If agreement is not reached, the eldest shall be the representative.

**A person who attends the written consent process and reads the written consent form and all documented information provided to a subject on behalf of the subject or their legally acceptable representative if they are unable to read the consent form, subject information sheet, and other documented information

***Principal investigator, or doctor, dentist, or oriental medicine doctor designated by the principal investigator