

Original Paper

An Overview of the Cure of HIV/AIDS Harbal Therapy Containing Natural Antioxidant, Vitamins and Minerals

Silas David Emmanuel^{1*}, I. M. Bugaje² & S. M. Mohammad³

¹ Kaduna Polytechnic Tudun Wada Kaduna State, Nigeria

* Silas David Emmanuel, Kaduna Polytechnic Tudun Wada Kaduna State, Nigeria

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Abstract

Purposes: The unprecedented and sequence through which an estimate of 25 million lives have gone to their early grave yard through Acquired Immune-deficiency Syndrome HIV/AIDS can never be quantified; since, when it was first describes in 1981. In 2017/2018 by (UNAIDS) it was estimated globally for about 36.9 millions people were living with Human, Immunodeficiency Virus (HIV) so to say. Henceforth the progress made in the field of treatment in the form of Antiretroviral Therapy (ART) disease has not been fully ascertain for the cure of HIV/AIDS; except, perpetual clinical suppressions. Thus, the current challenges that man kinds faces with the used of perpetual intake of antiretroviral therapy (clinical suppression)/artificial vaccine is un-justifiable. However, search for HIV therapy have open a new chapter in the search for novel drugs from Kaduna Polytechnic procedure. This review focuses on vitamins, antioxidant, mineral and supplement as sources of in-hibitors or eradications for human immunodeficiency virus type-1 (HIV) reverse transcriptase. **Objective:** To assess whether vitamins, antioxidant, minerals supplement are effective and safe in eradicating mortality and morbidity among populace with HIV infection. **Selection criteria:** Randomized control trials were selected that compared the effect of vitamins (A, C, D, E, K.), antioxidant, minerals and supplement with regard to treatment measures in HIV infected persons. **Methods:** To prevent authors bias, based on a systematic search of literature; anti-HIV reverse transcriptase activity of some plant's species like those of Eucalyptus leaves, Garlic fresh fruits, Baobab leaves, aloe vera, neem leaves, moringa leaves, bitter leaves etc. respectively. Thus, these medicinal plants contain an appreciable or above values antioxidant compound or photochemical like those of Phenolic, anthraquinone, tannin, falconoid, terpenoid, lignin, coumarins etc. respectively. Contrarywise, these phytochemical compounds have been exploited traditionally for the cure of many diseases as well as inhibition of viral replication/transcription. Further investigations have shared more light through which phytochemicals compounds inhibit virus replication either during the

viral entry inside the host cell or during their replication. **Originality:** in view of the current investigation or to accelerate drug discovery and innovation, this review recommends the urgent need to tap into the enrich locally available endogenous knowledge of putative anti- HIV/AIDS, photochemical and their derivatives, (reverse pharmacology, determine pan assay, interferences compounds, microbial enzyme metabolites relationship and their mechanisms to treat virial diseases.

Keywords

Vitamins, mineral, Photochemical secondary metabolite, microbial enzyme metabolite, HIV/AIDS

1. Chapter One

1.1 Introduction

The HIV epidemic is receding globally with a 38% drop in new infections (UNAIDS, 2014); however, it continues to pose as a major global public health challenge. The goal of an effective vaccine still remains elusive. Anti-Retroviral Treatment (ART) has increased the life span of People Living With HIV (PLHIV) and 14.9 million people globally are receiving ART (WHO, 2015). Even though the mainstream highly active anti-retroviral therapy (HAART) potently suppresses the plasma HIV-1 viral load, it is unable to eradicate HIV completely. Therefore, there is a lifelong requirement for ART which will decrease the morbidity due to drug toxicity and acquisition of resistance. Considering this, there is a continuous need to explore safe and efficacious anti-retroviral agents; which is a challenge that needs to be addressed through integrated approaches. Azidothymidine (AZT)—a NRTI drug was the first accidental breakthrough in HIV therapy in 1980's with its origin from cancer research on photochemical. Acyclovir, Val acyclovir and various HIV protease inhibitors are subsequent statutory examples following this trend. This can be attributed to the fact that the chemical novelty for chemical scaffolds in natural products is 40% higher than any other source. Although natural products are extensively studied for anti-HIV activity, majority of these studies are restricted to preliminary screenings that aren't pursued to the molecular level with allied approaches for substantiated outcomes.

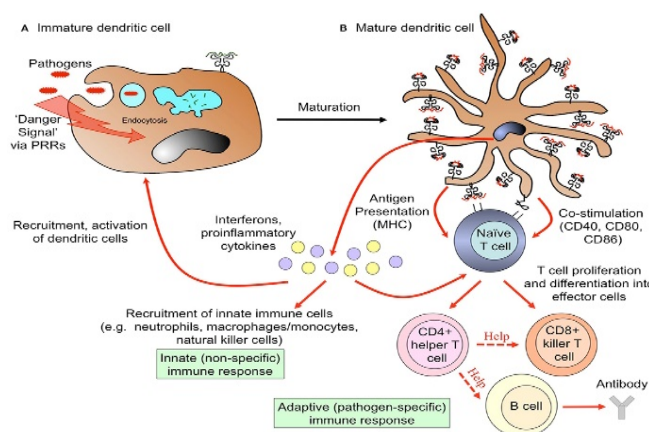


Figure 1 .Dendritic Cells Link Innate and Adaptive Arms of the Immune System. (A) Uptake of Pathogens and Recognition of Pathogen-Associated “Danger Signals” by Pattern Recognition

Receptors (PRRs) Triggers Dramatic Morphological and Functional Changes in DCs, Termed Maturation. These Changes Involve the Formation of Dendrites, Down-Regulation of Antigen Uptake, and Redistribution of Major Histocompatibility Complex (MHC) Molecules from Intracellular Endocytic Compartments to the Cell Surface. (B) Mature DCs Migrate to Draining Lymph Nodes and Present Information about the Invading Pathogen in the Form of Processed Peptides Loaded onto MHC Molecules to Naïve T cells. Upregulation of MHC and Co-Stimulation Molecules Enables Activated DCs to Initiate Adaptive T and B Cell Immune Responses, the Nature of Which Are Determined by the Cytokine Milieu. This Initiates the Cascade to an Adaptive Immune Response, Leading to Clearance of Infected Cells, and Extracellular Pathogens. Activated Mature DCs Also Secrete Interferons and Proinflammatory Cytokines That Recruit Circulating Innate Immune Cells to Provide Rapid Defense Against Infection

Nonetheless majority of HIV-1- infected individuals live in sub-Saharan Africa where malnutrition and food insecurity are a widespread condition. Malnutrition and weight loss in patients with HIV/AIDS are known to accelerate disease progression, increase morbidity and reduce chances of survival, due to the well-documented impact of malnutrition on immunity. The pathogenesis of AIDS related malnutrition and cachexia is multi-factored and includes food insecurity, reduced intake, malabsorption, reduced utilization of nutrients, the elaboration of proinflammatory cytokines, and endocrine and metabolic alterations combined with increased nutritional needs. There is now clear evidence that malnourished individuals starting ARV therapy are far more likely to die in a given period than well-nourished individuals. Weight loss and wasting remain significant clinical problems even in the current era of Highly Active Antiretroviral Therapy (HAART). The role played by dietary intake in HIV patients in resource-limited settings, both in those who are on antiretroviral treatment and those who are not, has hardly been studied at all, although the need to integrate HAART with food supplementation—to improve the patients’ diet—in areas of high food insecurity has been recognized. Some authors in certain countries in sub-Saharan Africa, where the AIDS epidemic co-exists with chronic food insecurity, have indicated the benefits of programs that aim to integrate the HAART therapy and food supplementation, in terms of weight increase, improved quality of life and a reduction of the adverse effects of the HAART therapy.

The first aim of this paper is to describe the main characteristics of the state of health and of nutrition and the adequacy of diet of among HIV infected patients worldwide, on HAART and not, all of whom were included on the food supplementation program me. Further aims are determining the appropriate sequence through which future research could result in interventions to improve micronutrient intake and status in HIV patients in general. Thus, it can also be invariably and immensely contributing to a reduction in the magnitude and impact of the global HIV epidemic. Such interventions are feasible and affordable, which do not require HIV testing facilities and may even be beneficial to people without

HIV infection. Finally, a particular emphasis on a widened and upgraded exploratory approach for minerals, vitamins and photochemical research using modernized tools to catalyze drug discovery for HIV and HIV associated co-morbidities.

2. Literature Review

2.1 The Basic Origin of HIV/AIDS Virus

The human immunodeficiency viruses 1 and 2 (HIV-1, HIV-2) originated from the simian immunodeficiency viruses (SIVs) of primates. Thus, HIV-1 and HIV-2 each had a zoonotic origin but now spread directly from human to human. HIV-1 was first isolated in 1983 and HIV-2 in 1986 and they represent two different epidemics. The SIV of chimpanzees (SIV_{cpz}) gave rise to HIV-1 in humans, and the SIV of the sooty mangabey monkey (SIV_{sm}) to HIV-2 in humans. It is still uncertain exactly how the transmission of these SIVs to humans occurred.

2.2 Types of HIV

There are Two major types of HIV which have been priorly identified they are as follows:

[16]: HIV-1: It is the basis of the international wide spread and is most usually mentioned to as HIV. It is an extremely adaptable virus, which transforms readily. There are many dissimilar straining of HIV-1, which can be categorized according to groups and subtypes; M and O. Within group M, there are currently known to be at least ten hereditarily dissimilar subtypes which are A to J. HIV-2: In adding, group O holds another distinct group of mixed viruses. HIV-2 is fewer pathogenic and occurs infrequently; it is found mostly in West Africa, European, Asian countries, etc., respectively.

HIV infection mechanism

HIV begins its infection by voluntary to the CD4 receptor on the host cell. CD4 is present on the surface of several lymphocytes, which are a serious part of the body's immune system. It is now known that a co-receptor is needed for HIV to enter the cell. Following combination of the virus with the host cell, HIV enters the cell. The genetic material of the virus, which is RNA, is free and undergo reverse transcription into DNA. An enzyme in HIV called reverse transcriptase is necessary to catalyze this change of viral RNA into DNA. Once the genetic material of HIV has been altered into DNA, this viral DNA enters the host cell nucleus where it can be combined into the genetic material of the cell. The enzyme integrate catalyzes this process. Once the viral DNA is incorporated into the genetic material of the host, it is promising that HIV may persist in certain latently infected cells is the chief barrier to eradication or cure of HIV.

2.3 Modes of Transmission

Modes of transmission

Infected Blood: HIV spread through contact with infected blood. HIV is transmitted through transfusion of contaminated blood or blood components.

Contaminated Needles: HIV is frequently spreading amongst operators by the distribution of needles or syringes contaminated with very minor amounts of blood from someone infected with the virus. Mother

to child: Women can transmit HIV to their offspring throughout gestation or birth. HIV can also be transmitted through in discriminate sexual intercourse women and about 90% of the infections is obviously from sexual intercourse

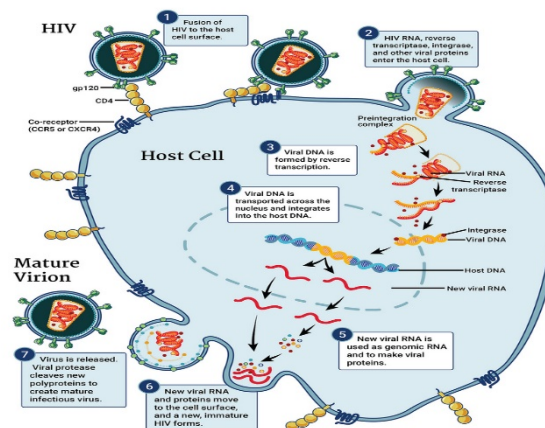


Figure 2. HIV Replication Cycle

2.4 Possible Effects and Current Knowledge

2.4.1 Primary HIV Infection

The effects of primary HIV infection on micronutrient status have not been studied. Nonetheless, it is conceivable that the acute HIV syndrome, with fever, anorexia, nausea, and diarrhea followed by weight loss, may impair micronutrient status. However, because the acute stage is transient, it is mainly of concern in individuals with prior poor micronutrient status or lack of access to an adequate convalescent diet. Such deficiencies, precipitated or exacerbated by a symptomatic primary HIV infection, could be pivotal by affecting the viral load set point and host defense and thereby affecting HIV transmission and progression.

2.4.2 Asymptomatic HIV Infection

Little acute phase response occurs during the long asymptomatic stage of HIV infection, but viral replication occurs continuously, leading to the slow but relentless increase in viral load over a number of years. Changes in the structure and function of the intestinal tract seem to occur relatively early in HIV infection. An HIV entero pathy characterized by villous atrophy and crypt hyperplasia and accompanied by malabsorption has been described in HIV-positive individuals. Reduced absorption likely leads to impaired micronutrient status at this stage, which may be important because of the stage's long duration.

Few studies on micronutrient status have been conducted with asymptomatic HIV-positive individuals and appropriate comparison groups. However, some studies have been done in developing countries in pregnant women attending antenatal care. HIV-positive pregnant women are usually at an early stage of infection, partly because even early HIV infection reduces fertility and increases fetal loss. Accordingly,

among 1669 Zimbabwean pregnant women, those with HIV infection had mean viral load of 3.85 log and morbidity, body composition and serum α_1 -antichymotrypsin similar to values for HIV-negative women. Nonetheless, serum retinol and β -carotene were considerably lower and α -tocopherol, ferritin and folate were slightly but significantly lower after adjustment was made for elevated acute phase proteins. These differences most likely reflect increased requirements in HIV-positive individuals but this could not be substantiated because intake was not controlled for.

In this developing country setting, most women seek antenatal care when pregnant and are rarely aware of their HIV status. Although selection bias is therefore not likely to be a problem, HIV-positive and -negative women may not have comparable socioeconomic backgrounds. Confounding cannot be excluded because poor socioeconomic status may be associated with unprotected sex and HIV infection and be a cause of poor micronutrient status. Controlling for dietary intake and possibly other socioeconomic factors is therefore critical.

2.4.3 Symptomatic HIV Infection

During symptomatic HIV infection, the effects of HIV in the gastrointestinal tract are more severe. The increasingly frequent enteric and other infections result in both acute phase responses and localized lesions which further exacerbate an impaired micronutrient status.

A number of early studies from developed countries, before the use of ARV drugs, reported low serum levels of several micronutrient indicators, such as vitamin A; aryltenoids; vitamins B₆, B₁₂, C and E; folate; as well as selenium and zinc in adults and children. However, these studies were mostly hospital based and contained little information about the stage of HIV infection and how HIV-positive and -negative controls were selected. Furthermore, the acute phase response was not controlled for, which leads to overestimation of the association between HIV and deficiencies for some of the micronutrients. Many patients may have taken supplements in response to their HIV diagnosis and confounders. This may have led to gross underestimation of the effect of HIV infection on micronutrient status, making it difficult to base conclusions on these data.

One study attempted to control for the intake of micronutrients and will therefore be mentioned in more detail. This cross-sectional study was conducted in 108 HIV-positive homosexual men in United States. Serum vitamins A, B₆, B₁₂ and E and serum zinc were assessed and compared with values for 38 HIV-negative homosexual men. All subjects were selected from hospitals, clinics or community programs. All were free from other diseases, but 19% of the HIV- positive men had symptoms and 90% had normal weight. HIV-positive men had higher triceps skin fold thickness than did the HIV-negative men. More HIV-positive men took supplements and had a higher total intake of all micronutrients than did HIV-negative men. In fact, most HIV-positive men had intakes above the recommended dietary allowance. Intakes at or above the recommended dietary allowance were associated with normal plasma levels in the HIV-negative men. In contrast, in HIV -positive men even intakes several times the recommended dietary allowances were not associated with adequate serum levels. No attempt was made to control for the acute phase response, and data were not given separately for subjects with and

without symptoms. The authors concluded that intake of nutrients at levels recommended for the general population did not appear adequate for HIV-1-positive men. Despite its limitations, this study has contributed considerably to the widespread notion that HIV-positive individuals need multiples of recommended dietary allowances.

Prevention and prompt treatment of opportunistic infections and effective ART will most likely reduce the effect of HIV infection on micronutrient status. For example, antioxidant status is considerably improved in patients on protease inhibitors. Nevertheless, drugs often have adverse effects, such as nausea, vomiting and diarrhea, or affect micronutrient metabolism, resulting in a negative effect on micronutrient status.

2.5 Sexual Transmission

Sexual transmission depends on infectivity of the HIV-positive individual as well as susceptibility of the exposed HIV-negative partner. No studies have addressed the effect of micronutrient intake and status in HIV-positive individuals and sexual transmission on clinical outcomes. However, a few studies addressed the relationship between micronutrient status and genital shedding of HIV. In a cross-sectional study of pregnant HIV-positive women in Nairobi, Kenya, low serum retinol was a predictor of HIV DNA in vaginal but not cervical secretions [26]. In contrast, no relationship was found between serum retinol and HIV RNA in cervicovaginal lavage in women in New York, USA. Similarly, low serum retinol was also a predictor of vaginal HIV shedding among non-pregnant HIV-positive women who attended a sexually transmitted diseases clinic in Mombasa, Kenya. In a subgroup of women in the same study, low serum selenium was also a predictor of vaginal HIV shedding after adjustment for the previously found effect of low serum retinol.

Three nested case-control studies addressed the role of vitamin A and other micronutrients regarding the risk of acquiring HIV infection for sexually active adults, with quite conflicting results.

In Kigali, Rwanda, a cohort of sexually active women was followed every 6 months for 24 months. No differences were noted for serum concentrations of retinol, carotenoids, vitamin E, ferritin and selenium between 45 women who seroconverted and 74 randomly selected women who did not. HIV-negative adults attending sexually transmitted disease clinics in Pune, India, were enrolled in a cohort and followed every 3 months for HIV infection. Serum retinol, various carotenoids and vitamin E concentrations were determined for 44 participants who later seroconvert and for 44 matched HIV-negative controls. The time between the visit when vitamin status was determined and the visit when the participant first was found to have HIV seroconvert was 6 months. Serum β -carotene below $0.075 \mu\text{mol/L}$ (i.e., the upper tertial) was associated with an increased risk of seroconversion (odds ratio [OR] 4.67; 95% confidence interval [CI] 1.34, 16.24), which increased further after adjustment for risk behavior, age and other confounders. Serum retinol and vitamin E were respectively associated with non-statistically significant increased (adjusted OR=2.96, $p=0.34$) and decreased (adjusted OR 0.35, $p=0.12$) risks of seroconversion. Finally, a study was conducted among sexually active men in Nairobi, Kenya. A cohort of HIV-negative men seeking treatment for an acute genital ulcer was established.

After treatment, the some men were tested for HIV infection at 3month intervals; mean follow-up time was 6 months. For each participant who seroconvert, two or three consecutive participants who remained HIV negative were included as controls. Surprisingly, although there were no differences in socioeconomic status and history of unprotected sex, the 38 sero-converters had higher baseline serum retinol values than did the 94 controls. Serum retinol greater than 0.70 $\mu\text{mol/L}$ was associated with a greater than two-fold increased risk of seroconversion. The authors suggest that the results may be due to an effect of vitamin A on differentiation of target cells of the monocyte/macrophage lineage in the mucosa, as previously reported.

2.6 Herbal Medicine

Herbal medicine

Preparations resulting from plants are mutual to many beliefs and a number of progressive medicinal drugs were derived from plants. There are herbs that can heal unsafe disease such as the cancer. Rarely is it said that where allopathic fails, herbal medicines work. Herbal medicines are said to work to such an amount that they can even do away with the need for the operation. In India the medicine of herbs came to be known as Ayurveda this form of medicine has used herbs to treat all forms of disease. A Number of medicinal herbs have been reported to have anti-HIV properties which are shown in Table 1.

2.7 New Drug Therapies for HIV

A recent review of HIV therapies with new mechanisms of action in phase 2 clinical trials has reported on drugs with new mechanisms of action, including histone deacetylase (HDAC) inhibitors, gene therapies, broadly neutralizing anti-HIV antibodies, immune modulation, and drugs with new mechanisms to block HIV entry. The new therapies are being developed for both as add-on therapy to existing combination antiretroviral therapy and as agents to be used during treatment interruption. The current drugs in development have had varying degrees of success in the early trials. Each of these new drugs may potentially fill a void in current Antiretroviral Therapy (ART) therapies, which will ultimately lead to improved outcomes in HIV-infected individuals.

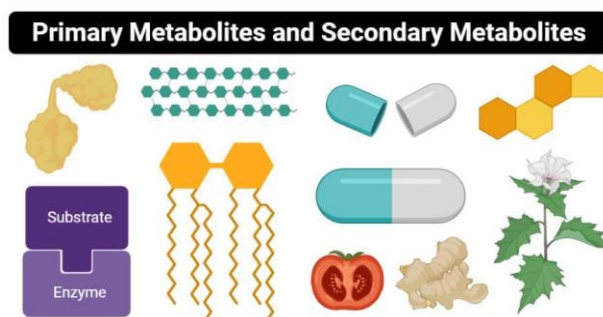


Figure 3. Posted Primary Metabolites vs Secondary Metabolites

2.8 Natural Products and Herbal Medicines for HIV

Although effective, ART is not without serious adverse events, which is especially evident in persons undergoing long-term treatment. In addition, the current therapies are limited by emergence of multidrug resistance, and new drugs and novel targets are needed to overcome the issues of HIV reservoirs in the body in order to have the complete eradication of HIV and AIDS. Latently infected cells remain a primary barrier to eradication of HIV-1. Over the last ten years the molecular mechanism by which HIV latency persists has led to the discovery of a number of drugs that are able to selectively reactivate latent proviruses without inducing polyclonal T cell activation [150]. Interestingly, histone deacetylase (HDAC) inhibitors, including vorinostat are able to induce HIV transcription from latently infected cells. Vorinostat has been shown to increase the susceptibility of CD4⁺ T cells to infection by HIV in a dose- and time-dependent manner, does not enhance viral fusion with cells, but increases reverse transcription, nuclear import, and integration, and enhances viral production in a spreading-infection assay. HDAC inhibitors, particularly vorinostat, are currently being investigated clinically as part of a “shock-and-kill” strategy to purge latent reservoirs of HIV.

Syed Ayaz Ali et al.,

Table 1. Locally Available Nigeria Endogenous Medicinalherba That Have Been Reported to HAVE Anti-HIV Properties

Plant	Potential	Example	Biochemical	Vitamins	Minerals	Therapy
Leaves/Fruits	Photochemical Virus		Synthesis			
	Tregetours					
Tomato	Glycoalkaloids	Nitrogen	Carotenoid's hydrocarbon	A, C K	Potassium	Antiviral
Garcinia Kola (Bitter cola)	phenolic compounds Alkaloid, Tannins Flavonoid, sterol anthraquinones	Nitrogen	Caffeine	A, C, E, B1, B2, B3	Iron (Fe) Calcium (Ca) potassium(K)	
Bitter leaf	Alkaloid Saponins Tannins, Flavonoid glycoside Sesquiterpene, anthraquinone	Nitrogen	Benzophenone, kola none, Kola flavanone	C, K		Antiviral
Neem leaf	Flavonoid, terpenoid, steroids	Nitrogen	Azadirachtin, Azadinone, Salanin Carotenoid, quercetin, Oleic acid	E & C	Calcium (Ca) iron (Fe), potassium (K) Magnesium (Mg) Phosphorus (P)	Antiviral

Mo	ringer	Alkaloid,	Saponin,	Nitrogen	Beta-carotene	C, B6 A D	Iron (Fe)	Antiviral
Oleifera		Flavonoid,	terpenoid,			E		
		phenol						
		Anthraquinone,						
		Glycoside						
Eucalyptus leaf		Sesquiterpenes,	Beta-	Nitrogen	-		Manganese	Antiviral
		triketone,	Beta-				Iron (Fe), Cupper	
		diterpene,	Steroidal				(Cu)	
		compound	Tannin				Potassium (K)	
		Flavonoid						
Turmeric		Curcuminoid,		Nitrogen	Curcuminoid,	C	Calcium (Ca), Iron	Antiviral
(Curcuma		terpenoid	phenol,		Beta-carotene		(Fe), Potassium(K)	
longa)		tannin					Phosphorus(p)	
Garlic		Alkaloid,	terpenoid,	Nitrogen	Ajoene, allicin,		Calcium (Ca), Iron	Antiviral
		Anthraquinone			allyl,		(Fe) Potassium (K)	
		Flavonoid					mangansae9Mn	

This period of “asymptomatic” infection differs

2.9 Naturally Derived Anti-HIV Agent or Microbial Enzyme by Product (Secondary Metabolites) as Antioxidant for Antiviral Drugs Therapy

The following natural products namely Calanolides (Coumarins), Betulinic acid (a Triterpene), Baicalin (a Flavonoid), Polycitone A (an Alkaloid), Lithospermic acid (a Polyphenolic) can be mentioned as promising for anti-HIV agents (whereas Withanolides (Steroidal lactones) for HIV-associated neurocognitive disorders

2.10 Coumarins

An example of non-nucleoside specific reverse transcriptase inhibitors (NNRTI) of the virus are calanolides which are a type of coumarin derived from different tropical tree species of the Calophyllum (Clusiaceae family). Calanolide A, Calanolide B and its derivative 7, 8-dihydrocalanolide B can prevent cytopathogenic effects of HIV-1 on host cells and are attained from the Calophyllum lanigerum. Cordatolide A and B are similar in structure to Calanolides and can inhibit replication of HIV-1. These compounds are extracted from the Calophyllum cordato-oblongum. Suksdorfia is another compound that also has inhibitory effects on replication of the virus in the T cell line and is a pyrocoumarin derivative that can be extracted from the Angelica morii and Lomatium suksdorfii fruits from the Apiaceae family as seen in table 1 and 4.

2.11 Terpenes

Antiretroviral activity with diverse mechanisms of action have been observed with some triterpenoids.

Betulinic acid and oleanolic acid tested in H9 lymphocyte cells have shown inhibition of HIV and can be obtained from the leaves of *Syzigium claviflorum*. Inhibition of HIV-1 replication in these cells were observed with oleanolic acid which can be attained from methanolic extract of the *Xanthoceras orbifolia*, wood from the Sapindaceae family. Potent inhibitory activity against HIV-1 protease has been seen with maslinic acid derived from the *Geum japonicum*. Anti-HIV replication activity in H9 cells is observed with Celastrol B that is derived from ethanolic extract of the *Celastrus hindsii* which is from the Celastraceae family. The protostanes, garsiterpenes A and C can suppress HIV-1 RTase activity and are obtained from the ethyl acetate extract of the stems and bark of *Garcinia speciosa*. Lanostane-type triterpene has also shown inhibition of HIV replication in H9 cells and is a suberosol obtained from ethanolic extract of the leaves and stems of *Polyalthia suberosa* from the Annonaceae family. Triterpene lactone, lancilactone C extracted from the roots and stems of *Kadsuralancilimba* is another compound that restrains HIV replication in these cells. The 12-O-tetradecanoylphorbol-13-acetate (TPA), a phorbol diester, can inhibit cytopathogenic effects of HIV-1 and is attained from methanolic extract of *Croton tiglium* from the Euphorbiaceae family as seen in table 1 and 4. Prostratin, a phorbol ester also has anti-HIV properties and is extracted from *Homalanthus nutans* from the Euphorbiaceae family.

2.12 Flavonoids

Favorable anti-HIV activity have been exhibited by flavonoids and associated polyphenols. They are known for having antioxidant properties and have been found to show antiviral activity in different cell cultures [42]. Baicalin (as seen in table 1 and 4) inhibits HIV replication in PBMC in a dose dependent fashion and is an anti-HIV flavonoid extracted from *Scutellaria baicalensis*. The 6, 8-diprenylaromadendrin and 6, 8-diprenylkaempferol, prenylated flavonoids, also show anti-HIV activity in the XTT-based, whole-cell screen and are derived from the extract of *Monotes africanus*. Flavonoid gallate ester and quercetin 3-O-(2-galloyl) α -L-arabinopyranose can inhibit integrase activity of HIV-1 and are obtained from ethanolic extract of *Acer okamotoanum* from the Aceraceae family. Hinokiflavone, robustaflavone, and biflavonoids have demonstrated inhibition of the polymerase of HIV-1 reverse transcriptase (RT) and are attained from methanolic extracts of leaves and twigs of *Rhus succedanea* from the Anacardiaceae family. Wikstroel B, a biflavonoid, also shows anti-HIV activity and can be isolated from extracts of roots of *Wikstroemia indica* from the Thymelaeaceae family. Xanthohumol, a prenylchalcone that has demonstrated inhibition of HIV-1 and is extracted from hops *Humulus lupulus*.

2.13 Alkaloids

Different types of alkaloids have shown anti-HIV activity. One of the natural products with interesting activity on RT is polycytone A (as seen in Table 1 and 4, an aromatic alkaloid isolated from the marine ascidian *Polycitor* sp. Polycytone A exhibits potent inhibitory activity on both RNA- and DNA-directed DNA polymerases. Papaverine, an alkaloid can inhibit HIV replication and is extracted from *Papaver somniferum* from the Papaveraceae family. Buchapine is a type of quinolone that has shown inhibition

of cytopathogenic effects of HIV-1 and is isolated from *Eodiaroxburghiana*. Nitidine also shows anti-HIV activity and is extracted from the roots of *Toddalia asiatica* of the Rutaceae family. A piperidine flavone related alkaloid O-demethylbuchenavianine shows a hindrance to the activity of HIV and is attained from *Buchenavia capitata* of the Combretaceae family. Harmine has shown inhibition of HIV replication in H9 cells and is derived from *Symplocos setchuensis*. 1-Methoxy canthionone has anti-HIV properties and is obtained from *Leitneria floridana*. Hypoglaumine B, Troponine B, and Troponine A are sesquiterpene pyridine alkaloids that have shown to also possess anti-HIV properties and are isolated from *Tripterygium wilfordii* and *Tripterygium hypoglaucum*.

2.14 Phenolics

Because of heightened phytohaemagglutinin-induced lymphocytes proliferation, prolonged administration of polyphenol-rich fruit juices is believed to be promising to HIV-positive individuals. There are several tannins and related phenolic substances which show virucidal effects in several viral systems. Lithospermic acid isolated from *Salvia miltiorrhiza* has strong anti-HIV activity in H9 cells. Punicalagin, chebulagic acid, and punicalin are hydrolysable tannins that demonstrate anti-HIV activity and come from *Terminalia chebula*. Repandusinic acid has shown inhibition of HIV-1 RTase and is extracted from *Phyllanthus niruri* of the Euphorbiaceae family. Monopotassium and monosodium salts of isomeric caffeic acid tetramer have shown inhibition of HIV replication and are obtained from the aqueous acetone extract of *Arnebia euchroma* of the Boraginaceae family. Camellia-tannin H shows inhibition of the HIV-1 protease and is extracted from the pericarp of *Camellia japonica*. Galloyl glucoses and gallic acid exhibited a hindrance of HIV integrase and are extracted from *Terminalia chebula* of the Combretaceae family. Mallotojaponin is a dimeric phloroglucinol derivative that inhibits activity of HIV-1 RTase and is extracted from the pericarps of *Mallotus japonicus*. The curcuminoids have shown inhibition of HIV-1 and HIV-2 protease and are extracted from rhizomes of *Curcuma longa*. Peltatol A is a prenylated catechol dimer that shows anti-HIV activity and is extracted from *Pothomorphe peltata* of the Piperaceae family.

2.15 Lignans

Several lignans have antiviral properties. Phyllamyricin B and its lactone retrojusticidin B display inhibition of HIV-RTase activity and are obtained from chloroform extract of *Phyllanthus myrtifolius*/P. urinaria of the Euphorbiaceae family. Anolignan B, anolignan A, and dibenzylbutadiene lignans have shown inhibition of HIV-1 RTase and are extracted from *Anogeissus acuminata*. Gomisins have been found to be one of the strongest inhibitors of HIV replication and is obtained from *Kadsura interior*.

2.16 Quinones

Plumbagin, 1, 4-naphthoquinone, juglone, and vitamin K3 are naphthoquinones that all demonstrate HIV inhibitory activity. Conocurvone is a trimeric naphthoquinone that shows effective anti-HIV activity and is extracted from *Conospermum incurvum* of the Proteaceae family.

2.17 Saponins

Actein is a tetracyclic triterpenoid saponin that exhibits strong anti-HIV activity and derives from the rhizome of *Cimicifuga racemosa* (black cohosh).

2.18 Xanthones

Swertifranchetide is a flavonone–xanthone glucoside that has shown inhibition of HIV-1 RTase and is extracted from *Swertia franchetiana*. Macluraxanthone B is a prenylated xanthone that also shows anti-HIV activity and is extracted from *Maclura tinctoria* of the Moraceae family.

Table 2. Differences Between Primary Metabolites and Secondary Metabolites

Basis Comparison	Primary Metabolites	Secondary Metabolites
Definition	Primary metabolites are the compounds that are directly involved in the metabolic pathways of an organism necessary for its growth, development, and reproduction.	Secondary metabolites are the organic compounds that are produced by various organisms that are not directly involved in the growth, development, or reproduction of the organism but are essential in the ecological and other activities.
Also termed	Primary metabolites are also termed as central metabolites.	Secondary metabolites are also termed as specialized metabolites.
Growth phase	Primary metabolites are produced during the growth phase of the organism.	Secondary metabolites are produced during the stationary phase of the organism.
Quantity	This phase of growth is also termed as “trophophase”.	This phase of growth is also termed as “idiophase”.
Extraction	Primary metabolites are produced in large quantities.	Secondary metabolites are produced in small quantities.
Specificity	It is easier to extract primary metabolites.	It is difficult to extract secondary metabolites.
Involved in	Primary metabolites are not species-specific and thus might be identical in some organisms.	Secondary metabolites are species-specific and thus are different in different organisms.
	Primary metabolites are involved in the growth, development, and reproduction of organisms.	Secondary metabolites are involved in ecological functions and species interactions.

Structural component	Primary metabolites might form the molecular structure in organisms.	Secondary metabolites are not a part of the molecular structure of the organism
Importance	Primary metabolites are used in various industries for different purposes.	Secondary metabolites are used in various biotechnological procedures for the formation of drugs and other compounds.
Defensive action	Primary metabolites are not active in the defense mechanism.	Secondary metabolites are active against foreign invaders and might be involved as a defense mechanism.
Examples	Examples of primary metabolites include proteins, enzymes, carbohydrates, lipids, vitamins, ethanol, lactic acid, butanol, etc.	Some examples of secondary metabolites include steroids, essential oils, phenolics, alkaloids, pigments, antibiotics, etc.



Plate 1. Posted Harvesting Aerobic Primary/Secondary Metabolite at Exponential/Exponential/Stationary Phase in Readiness for Divine Naija Herbal HIV Therapy

2.18 The Role of Oxygen in Normal of Unicellular Aerobic Organisms e.g., Viruses Against the Host

2.19 THE OXYGEN PARADOX

Oxygen is essential to sustaining normal cell function, and ultimately, aerobic life. All living aerobic organisms require dioxygen as an electron acceptor for efficient energy production and a signaling molecule in biological processes. However, it is constantly facing a paradox in which the breakdown of its products may be detrimental to cell function and survival.

Ever since the term ‘radical’ was introduced, there have been innovative developments in the science of medicine and physiology. Free radicals are chemically unstable species. In general, free radicals are atoms or molecules with an open shell, unpaired electron configuration generated by an incomplete one-electron reduction. These unpaired electrons are highly reactive, and can go on to activate a wide-range of mechanistic pathways, thereby inflicting much damage [58].

2.19.1 Reactive Oxygen Species

Oxygen is central to the generation of ROS. ROS can participate as beneficial molecules through cell signaling processes, but also as detrimental through inducing irreversible cell damage and death [14/56]. ROS production is initiated with the rapid uptake of oxygen and the subsequent activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, catalyzing the synthesis of superoxide anion ($O_2^{\cdot-}$). The chemically unstable ROS byproducts from aerobic cellular metabolism react almost instantaneously with neighboring species in their vicinity. The interaction of these stability-seeking agents causes them to propagate a cascade of reactions. This can then activate patho-physiological processes in the surrounding environment, which may ultimately disrupt and damage living cells, and potentially, cause tissue injury. There are a variety of reactive species, some of which include hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^{\cdot}), as well as the common ROS subclass – reactive nitrogen species – such as nitric oxide (NO^{\cdot}), nitric dioxide (NO_2^{\cdot}) and peroxynitrite ($ONOO^{\cdot}$). Although the physiological function of the cellular membrane is to act as a permeability barrier, separating the intracellular and extracellular environments, some ROS, such as H_2O_2 , are able to penetrate through the membrane barrier. Once inside the cell, ROS can be oxidized even further and elicit their effects. Therefore, reducing oxidants to physiological levels presents a complicated task.

2.19.2 Antioxidants

Antioxidants are either naturally occurring or synthetic bimolecular that prevent free radical induced damage by averting the formation of radicals, scavenging them, or promoting their decomposition in the body. Their neutralizing capabilities reside in their ability to donate an electron to ward off the deleterious effects of the highly reactive radicals or by converting ROS into different, less harmful, molecules. Antioxidants come in a variety of forms, ranging from those generated endogenously by the body to others administered exogenously as dietary supplements. When the natural balance between oxidants and antioxidants within the body is disturbed *via* antioxidant deficiency or increased ROS production, oxidative stress results. The subsequent adverse effects have appeared to be diminished, and sometimes resolved, through bodily antioxidant defense and supplementation.

A Free radicals once again is a molecules that contain an unpair electron in it outer orbit and that can exist independently or rather free radical are unstable atomic/molecule species because of their one or more unpaired electron. There minimizing the influence of free radicals requires an antioxidant. Antioxidant can be divided in to two forms they are as follows:

Synthetic

Natural

2.19.3 Synthetic Antioxidant

The use of synthetic antioxidants is quite hazardous for health because of its side effect, and it is however more or less use in the production of Antiretroviral viral therapy (ART) for HIV carrier patients and Covid-19 artificial vaccine. Thus, it has been reported to be quite hazardous and side effect. The side effect caused by using synthetic antioxidant when it lingers in the body is liver swollen, diabetes, high blood pressure, piles etc. respectively.



Plate 2. Posts the Researcher and the Village Head of Ishibori Trying to win His Heart on the Divine Herbal Therapy

d. Natural antioxidant

The use of natural antioxidant is by far much safer and beneficial for health and has much lower toxicity as seen in table 1, Some studies have been reported that supplement with vitamins C, E and antioxidant or antioxidant mixture can reduce symptom or indicators of oxidative stress as a results of exercise. Exercise training seems to reduce the oxidative stress of exercise such that train athletes showed less evidence of lipid peroxidation

c. Oxidative Stress

Excessive levels of ROS may be generated through over stimulation of the otherwise tightly regulated NADPH oxidase or by other mechanisms that generate ROS in a nonregulated fashion. An overload of free radicals and oxidants leads to their accumulation in the body, a phenomenon known as Oxidative Stress (OS). Generally, free radical production is counterbalanced by several mechanisms that include both enzymatic and non-enzymatic antioxidants. However, in times of imbalance between ROS and the body's antioxidant scavengers, OS ensues. OS may be a consequence of excess ROS production and/or reduced antioxidant capacity. The inability of the human biological system to detoxify and reduce oxidants or to repair detrimental damage disrupts physiological homeostasis. OS has been implicated in the pathogenesis of many other human diseases including cancer, diabetes, Parkinson disease, and even

AIDS.

Table 3. Clinical, Trials and Recommendations Offered by Different Communities in Some Local Government Areas, Offices Markets Regarding to the Newly Discovered Diving Fermented Naija HIV/AIDS Therapy for, Months and Years

STATE	Clinical Trials on Humanity	Strength of Recommendation	Adverse Effect	Other Aliments Gone	Death	HIV/COVID-19	Allergic Reactions
OYO STATE:							
IITA Ibadan	Over 50 persons	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, High blood reduce, Pile, Ulcer,	NIL	Gone	Nil
British American/Tobacco Company	Over 50 persons	Strongly Recommended	NIL	High blood reduce, Pile, Ulcer, High blood reduce , Pile, Ulcer,	NIL	Gone	Nil
KADUNA STATE:							
Kurmin/Mashi	Over 50 persons	Strongly Recommended	NIL	High blood reduce, Pile, Ulcer, High blood reduce , Pile, Ulcer,	NIL	Gone	Nil
Kaduna Poly	Over 50 persons	Strongly Recommended	NIL	High blood reduce, Pile, Ulcer	NIL	Gone	Nil
KASUBDA	Over 50 persons	Strongly Recommended	NIL	High blood reduce, Pile, Ulcer, High blood reduce , Pile, Ulcer,	NIL	Gone	Nil
Immigration Service	Over 50 persons	Strongly Recommended	NIL	High blood reduce, Pile, Ulcer, High blood reduce , Pile, Ulcer,	NIL	Gone	Nil
Zonkwa	Over 50 persons	Strongly Recommended	NIL	High blood reduce , Pile, Ulcer/ High blood reduce , Pile, Ulcer,	NIL	Gone	Nil
Kachia	Over 20 persons	Strongly Recommended	NIL	High blood reduce , Pile, Ulcer High blood reduce , Pile, Ulcer, Asthma,	NIL	Gone	Nil
Kafanchan	Over 10 persons	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer High blood reduce, Pile, Ulcer,	NIL	Gone	

Madakiya	Over persons	50	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer Asthma	NIL	Gone	Nil
NAFDAC	Over persons	30	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, High blood reduce, Pile, Ulcer,	NIL	Gone Nil	
NARICT	Over persons	20	Strongly Recommended	NIL	High blood reduce , Pile, Ulcer, Asthma, High blood reduce , Pile, Ulcer,	NIL	Gone Nil	
NILEST	Over persons	30	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer High blood reduce, Pile, Ulcer,	NIL	Gone Nil	
CROSS RIVER								
Ogoja/	Over persons	50	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer	NIL	Gone Nil	
Obudu	Over persons	50	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, High blood reduce, Pile, Ulcer,	NIL	Gone	Nil
Ishibori	Over persons	50	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, High blood reduce, Pile, Ulcer,	NIL	Gone	Nil
Igalo	Over persons	50	Strongly Recommended	NIL	High blood reduce, Pile, Ulcer, High blood reduce , Pile, Ulcer,	NIL	Gone	Nil
ADAMAWA STATE								
Mautech Yola	Over persons	50	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, High blood reduce, Pile, Ulcer,	NIL	Gone	Nil
NIGER STATE								
FUT Minna	Over persons	50	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, High blood reduce, Pile, Ulcer,	NIL	Gone	Nil
KANO STATE								
Federal secretariat	Over persons	30	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, High blood reduce, Pile, Ulcer, cough/catarrh all gone	NIL	Gone	Nil

KATSINA STATE								
Bugaje	Over persons	50	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer High blood reduce, Pile, Ulcer,	NIL	Gone	Nil
Kaita	Over persons	15	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer High blood reduce, Pile, Ulcer,	NIL	Gone	Nil
JIGAWA STATE								
FUT Duste	Over persons	15	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer, Asthma,	NIL	Gone	Nil
PLATEAUS STATE								
Bassa	Local	Over	15	Strongly	NIL	High blood reduces, Pile,	NIL	Gone
Government Area		persons		Recommended		Ulcer,		
ABUJA FEDERAL CAPITAL								
German Embassy	Over persons	15	Strongly Recommended	NIL	High-blood reduce, Pile, Ulcer,	NIL	Gone	Nil
American Embassy	Over persons	15	Strongly Recommended	NIL	High-blood reduce, Pile, Ulcer,	NIL	Gone	Nil
Biotech	Center	Over	30	Strongly	NIL	High blood reduces, Pile,	NIL	Gone
Abuja		persons		Recommended		Ulcer,		Nil
British (England)	Over Persons (White men)	12	Strongly Recommended	NIL	High blood reduces, Pile, Ulcer,	NIL	Gone	Nil
BORNO STATE								
Biu	Over Persons (White men)	12	Strongly Recommended	NIL				

Note. Asthma, Arthritis, hepatitis, smooth soothing breath excellent, cough/catarrh, Pneumonia etc., respectively all gone.

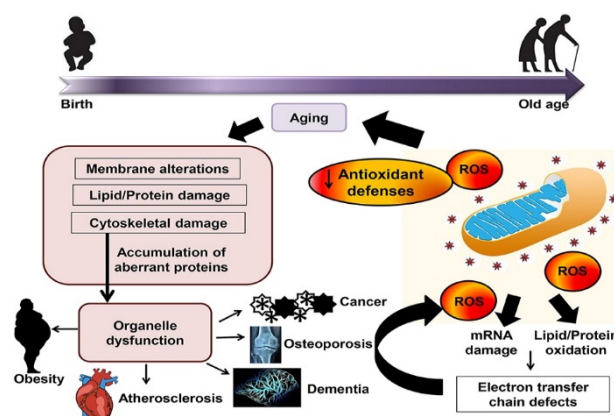


Figure 4. Effect of Oxidative Stress and the Interaction of Aging and Age-Related Diseases. Accumulation of Reactive Oxygen Species (ROS) Leads to mRNA Damage and Lipid/Protein Oxidation and Subsequently Causes a Decrease in Mitochondrial Function, and Ultimately Produces More Oxidative Stress. Mitochondrial Function Decline and Oxidative Stress Response in Aging may Subsequently Contribute to Age-Related Diseases

2.20 HIV: An Oxidative Role

AIDS is a particularly insidious disease with HIV compromising immune function. Rather than competing with the immune system, the virus targets for complete destruction. One of the key focuses of HIV is for annihilation of helper

T-lymphocytes (CD4 cells), which provide receptor sites for HIV to bind. The competition between HIV and helper CD4 cells commences as the virus accumulates in the lymph nodes. There the virus multiplies at an extraordinarily high rate. At the same time, the helper CD4 cells are proliferating at a great rate. However, the degree at which the virus is generated is much greater to that of the CD4 cells. It is believed that HIV does not kill by gradually undermining the immune system's ability to produce helper CD4 cells, but rather by overwhelming the finite regenerative capacity of the system. Furthermore, AIDS is triggered when the infecting virus mutates and diversifies into so many different strains that the immune system is suddenly overpowered. The diverse variations of HIV strains are different enough from the original to elude the immune system.

Ever since its first isolation in 1984, HIV has generally been accepted as the causative agent of AIDS. However, the discovery of HIV also led to a broadening of the view that ROS play a critical role in the expression of HIV and the development of AIDS. It has been reported that the virus induces OS by disturbing cellular antioxidant defense and initiating oxidative reactions. Advanced cases of HIV infection render individuals susceptible to opportunistic infections, which take advantage of the progressive immunodeficiency caused by HIV. Since cellular redox status is a normal physiological variable, any imbalance may elicit cellular response through proliferation, transcriptional activation, or apoptosis. For this reason, recent reports suggest that OS is a principal mechanism in the progression of AIDS.

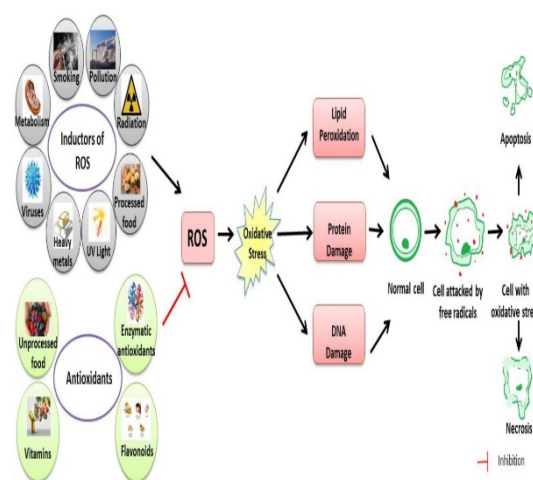


Figure 5. Posted Schematic Figure of the Link between ROS, Oxidative Stress and Their Effects on the Human Body. Oxidative Stress Is the Imbalance That Occurs When there Is an Increased Production of Free Radicals That Exceeds the Body's Ability to Neutralize It. Alteration of Chemical Reactions at the Cellular Level Leads to the Appearance of Free Radicals and Peroxides that Affect the Intracellular Structures – Proteins, Lipids, DNA, with the Disruption of Intrinsic Mechanisms at This Level. Free Radicals Are Normally Produced in the Body Due to the Influence of External Factors, such as Pollution, Cigarette Smoke, Virus (HIV/Covid-19) or Internal, Due to Intracellular Metabolism When Antioxidant Mechanisms Are Exceeded

a. CD4⁺ Depletion

Cellular CD4 immunodeficiency at an early stage is a hallmark of HIV infection. Several antigens may bind to receptor sites and trigger apoptosis in CD4⁺ T-cells. Apoptosis is a normal process of programmed cell death that the body utilizes in destroying infected cells. However, when T-lymphocytes become infected, their elimination results in a weakened immune function at a time in which the body needs it most. The body is faced with a dilemma of promoting apoptosis to eliminate HIV, yet consequently lowering the body's resistance to HIV.

Since OS can induce apoptosis, ROS may trigger apoptotic pathways responsible for the initial T-cell depletion upon HIV infection. A study that examined the relationship among CD4⁺ T-cell count, spontaneous apoptosis, and Fas expression from HIV-1 infected patients found an increase in both Fas expression and apoptosis, which was consistent with CD4 depletion [25]. Aires *et al.* support these findings, noting a significant increase in Fas expression on CD4⁺ T-cells from HIV-positive individuals compared to HIV-negative individuals. Therefore, increased Fas expression on CD4⁺ T-cells and OS at the time of infection correlate to the elevated levels of apoptosis found in HIV infected individuals, and hence, T-cell depletion in HIV disease. This phenomenon has been well documented to enhance disease progression [26/66]. If it were possible to suppress ROS levels at the onset of infection through antioxidant treatment, this would reduce Fas expression, activated apoptotic pathways and T-cell depletion, thereby slowing disease progression.

b. Macrophages

Macrophages are white blood cells derived from monocytes. They play a protective role by engulfing and digesting cellular debris. In times of infection, macrophages dispose of pathogens and enhance immune system response by stimulating lymphocytes. Macrophages are among the first cells infected by HIV. They are thought to serve as a reservoir, protecting HIV from neutralizing antibodies, and to bud HIV-1 primarily at the plasma membrane. Macrophages can then transfer the virus during activation of other immune cells. While T-cells die within a few days of HIV infection, macrophages appear to exist for months, continuing to release HIV. It has been shown that transmission of HIV from macrophages to CD4⁺ T-cells occurs rapidly. In addition, activation under OS conditions during HIV-infection were found to enhance inflammatory response and impair phagocytic response, causing ineffective clearance of apoptotic cells and the establishment of a chronic inflammatory state [70]. Both of these may be causative reasons behind the large T-cell depletion seen at the early stages of infection.

c. Tat

The transactivator gene (*tat*) of HIV encodes for the tat protein that activates immature T-lymphocytes. Tat is thought to be responsible for the burst of HIV replication that occurs when infected T-lymphocytes are stimulated. This gene is unique in that it is composed of two separate segments of DNA within the genome. Mutant strains of HIV that lack *tat* react far less actively when antigens stimulate the T-lymphocytes. Tat transforms T-cells into host cells suitable for HIV infection. It is believed that the gene encodes a protein that increases the expression of HIV genes leading to an increase in viral synthesis. Elevated levels of *tat* have been reported during times of HIV-infection, enabling proliferative infection of neighboring cells. Tat can also act as a toxin in uninfected cells, activating cell death pathways. The rapid spread of infection depletes T-cells and contributes to the progressive deterioration of the immune system in HIV disease.

Tat is known to increase HIV transcription rates. It is thought to bind to cellular factors and mediate their phosphorylation. This results in an increase in transcription of all HIV genes. Tat has been shown to induce OS. One study revealed that *tat* protein expression from HIV-1 infected HeLa cells amplified the activity of tumor Necrosis Factor (TNF), which stimulated HIV-1 replication through the activation of nuclear factor-kappa B (NF- κ B). Furthermore, this report found NF- κ B activation to be involved in the formation of reactive oxygen intermediates, while suppressing the expression of Mn-dependent superoxide dismutase (Mn-SOD) involved in the cellular defense system against OS. Specifically, the C-terminal region of HIV-1 *tat* suppressed Mn-SOD expression. This induced pro-oxidative condition was reflected in a lowered ratio between reduced and oxidized glutathione. These findings suggest that *tat*-mediated events affect cellular redox state, and that antioxidant therapy may potentially deplete oxidant levels, reducing NF- κ B activation, transcription of HIV, and disease progression.



Plate 3. Plate Posted Late Chief George Bengiashuye Agba and the Retired Peter Agba Who Lodge the Researcher in Kuciana Hotel

d. NF- κ B Regulation

OS has been implicated in increased HIV transcription through the activation of NF- κ B in HIV-infected patients. NF- κ B is a transcription factor that controls the transcription of DNA. Its activation is closely modulated by the redox state in the cell. In the cytoplasm, NF- κ B is bound to an inhibitory factor (I κ B) in its inactive form. However, a prooxidant state has been shown to release I κ B, thereby activating NF- κ B. This permits NF- κ B to translocate into the nucleus, where it binds to DNA and transcription of HIV can take place.

It is suggested that a reduction in the elevated oxidant levels found in the cytoplasm upon infection may be attained through antioxidant treatment. Subsequently, NF- κ B would remain bound to I κ B and unable to pass through the nuclear membrane to transcribe. Glutathione, a major intracellular thiol, has been associated with inhibition of NF- κ B by scavenging free radicals within the cytosol. Since Fas activation is associated with NF- κ B, inactivation or impairment of the Fas membrane receptor's binding site may not only lower levels of CD4⁺ T-cell depletion, but also reduce HIV transcription rates. This could potentially decrease disease progression.

Table 4. Locally Available Nigeria Endigenous Medicinal Herbs That Have Been Reported to Have Anti-HIV Properties

PLANT LEAVES/FRUITS	POTENTIAL PHYTOCHEMICAL OF TREGETOUS'	EXAMPLE	BIOCHEMICAL SYNTHESIS/BIOREACTIVE COMPOUNDS	VITAMINS	MINERALS	TH
Acacia Nilotic a (Bagaruwa)	Tannins Flavonoids	saponin, Nitrogen	Typtamine, Glutamy-lasparagine,	A, B, K	Ca,Na, Fe, Ant K, Mn, Zn,	

	Anthraquinones, Alkaloids, Terpenes, Steroids		Spirostane-saponin, Glutamy-lasporogine		P,	
Jute (Rama)	Tannins saponin, Nitrogen Flavonoids Anthraquinones, Alkaloids, Terpenes, Steroids, glycosides Carotenoid		Hemicellulasses, soluble lignin, isoquercetin, oleanolic acid, Arabinogalatan	B6, A, C, E	Fe, Zn, K, Na Ca Mg, Mn	Ant
Acacia gum (Arabic Gum) (Karo)	Tannins saponin, Nitrogen Flavonoids Terpenoids, Cardiac-glycosides		Carotenoids, P-Coumaric acid, Ferulic acid, caffeic acid	C, E, A	Mn, Ni, Fe Zn K, Cad	Ant
Allium cepa Onion	Glycosides, Alkaloids, Nitrogen Saponin, Quercetin, Flavonoids		Organosulfur, Fructans, Furctodigosa-ccharise	C E	Ca, Fe, Folate, Mg P K Na	Ant
Taura Fruit	Tannins saponin, N Phytosterols, Flavonoids, Steroids, Terpenoids, Triterpenoids			B1, C, A	Zn, Ca, Fe	Ant
Lemon grass	Tannins saponin, N Flavonoids, phenols, Alkaloids, Terpenoids, Steroids, glycosides Carotenoid, resin		Cardiotonic Properties, Gallic Acid Folate	A, C, Folate	Ca, mg, Fe, K, P Mn Zn Na	Ant

2.21 Antioxidants: A Therapeutic Approach

AIDS presents a vexing, yet extremely complicated, disease with many facets and implications. OS following HIV-infection depletes CD4⁺ T-cell count through apoptosis, while also enhancing HIV replication and transcription. These processes seem to rely upon the activation of NF-κB during redox impairment. A recent study found a significant depletion in antioxidant levels of vitamins A, C and E in HIV-positive children. It was suggested that an increase in OS from free radicals overwhelmed the antioxidant system. Furthermore, studies support that antioxidant deficiency leads to a more rapid HIV-associated disease progression. Since oxidative agents and antioxidant deficiency have such a tremendous role in advancing disease, researchers believe that antioxidant supplementation may

suppress HIV viral loads, thereby restoring immune function and potentially slowing the progression of AIDS.



Plate 4. Posted Process Fermented Divine Enrich Blood Tonic in Powder Form before Encapsulation

2.22 Conditions Linked to Perpetual Oxidative Stress for (HIV/COVID-19) Infected Patients Under Antiretroviral Therapy/Higher Active Antiretroviral Therapy (ART/HAART)

Oxidative stress may play a role in the development of a range of conditions, including:

- cancer
- Pile,
- Persistence Typhoid fever
- Cough
- **Alzheimer's disease**
- **Parkinson's disease**
- **diabetes**
- cardiovascular conditions such as **high blood pressure, atherosclerosis, and stroke**
- inflammatory disorders
- **chronic fatigue syndrome**
- **asthma**
- **male infertility**

2.23 Micronutrients, Immunity & HIV/AIDS

B. Vitamin A

Vitamin A is a group of fat-soluble compounds that plays an important function in bone growth, reproduction, vision, cell division, and cell differentiation. It is an essential component of the immune system that regulates white blood cell production to prevent, thwart off, and destroy bacteria and viruses that cause infection. Vitamin A is stored in the liver and is made up of two classes: preformed

vitamin A and provitamin A carotenoid. Preformed vitamin A is absorbed in the form of retinol. It is found in the liver, milk and animal foods, and is the most readily used form by the body. Provitamin A carotenoids are those that can be converted Vitamin A. Carotenoids can be found in colorful fruits and vegetables. Beta-carotene has shown a provitamin role in vitamin A deficiency, as it is the most efficient form made into retinol. Studies have suggested an antioxidant function of beta-carotene in reducing free radicals.

Vitamin A deficiency has been shown to induce OS. Moreover, most HIV-infected individuals present this condition, especially children and pregnant women. Most AIDS-related deaths and growth failure cases in HIV infected children have been found to be associated with vitamin A deficiency. Vitamin A therapy in Disinfected children has shown protective effects against morbidity and mortality by lowering respiratory tract infection and severe diarrhea. Several observational studies of HIV-infected pregnant women have displayed low serum vitamin A levels with an increased risk of mother-to-child transmission (MTCT). One study assessed the effect of antenatal vitamin A supplementation on the risk of MTCT from HIV infection. Although findings suggest that vitamin A deficiency is associated with MTCT, its role in lowering MTCT rates is insignificant.

A recent systematic review examining randomized controlled trials of HIV-infected women confirmed this result. The five trials included 7528 women and showed no evidence of a positive effect on prenatal and/or postnatal vitamin A supplementation for the risk of MTCT of HIV. Interestingly, prenatal vitamin A treatment was found to significantly improve birth weight. Nevertheless, the review suggested that data does not support vitamin A supplementation for HIV-infected women, despite the improvements in birth weight. Proper dosage and duration may play a role in these results.

Furthermore, while reports suggest a beneficial role for carotenoid supplementation in treating diseases associated with OS, clinical studies have observed harmful effects. One report suggested that the carotenoid cleavage products formed during oxidative attack might alter the course of ant oxidative action. It seems certain that because vitamin A is essential in immune response of macrophages, which are one of the first cells at the onset of HIV-infection, it may significantly, directly or indirectly, be responsible for the depletion of a large number of CD4⁺ T-cells and disease progression. Therefore, studies analyzing both the pharmacokinetics and pathogenesis of how vitamin A deprivation causes immunodeficiency in HIV-infected patients are necessary for potential therapeutic use.

▪ B vitamins

Deficiencies of thiamin, riboflavin and niacin, which are part of the coenzymes in the tricarboxylic acid cycle, are manifested by lack of energy, and these deficiencies may be partially responsible for the lack of energy commonly affecting HIV-infected persons. These deficiencies are aggravated by hyper metabolism, malabsorption and anorexia during the course of the disease. Deficiencies of thiamin, riboflavin and niacin, also termed vitamins B₁, B₂ and B₃, have been observed in HIV-infected individuals, even in early asymptomatic stages. Adequate intake and metabolism of the B vitamins is critical for the oxidation of energy-releasing nutrients (protein, carbohydrate and fat), and for

mitochondrial membrane protection during the energy conversions in the citric acid cycle and the electron transport system in the cellular mitochondria. B₆, B₁₂ and especially folate, are the main methyl donors to prevent accumulation of homocysteine in blood, a risk factor for cardiovascular disease. Although the majority of the epidemiological and observational studies on the association between HIV disease and the B vitamins were conducted in pre-ART patients, Guaraldi *et al.* conducted a cross-sectional observational study in 567 HIV-infected patients on stable ART. The study evaluated the relationship of homocysteine with the presence of cardiovascular risk factors. Higher levels of homocysteine in blood were significantly associated with the metabolic syndrome, lipodystrophy, higher blood pressure, waist circumference and waist-to-hip ratio, total lean body mass, visceral adipose tissue (VAT), VAT/total adipose tissue, homeostasis assessment model of insulin resistance (HOMA), triglycerides, high-density lipoprotein cholesterol, apolipoprotein A1, B, creatinine and 10-year cardiovascular risk but not with the use of ART.



Plate 5. Posted Divine Fermented Encapsulated Immune Booster for HIV Supplement

Observational studies in the pre-ART era found that low plasma levels of vitamins B₆ and B₁₂ were widespread in people with HIV infection. Approximately half of the HIV/AIDS patients were deficient in vitamin B₆, a condition associated with decreased Natural Killer (NK) cell activity, and neuropathies. A quarter of patients were deficient in vitamins B₁₂ and two thirds were deficient in folate. The majority of the effective formulas used in RCTs described in included a combination of B vitamins at the Recommended Dietary Allowance (RDA) levels (RDA thiamine = 1.1 mg/day for women and 1.3 mg/day for men; RDA riboflavin = 1.1 mg/day for women and 1.3 mg/day for men; and RDA niacin = 14 mg/day for women and 16 mg for men) or at several times the RDAs (thiamin doses at 20 and 24 mg/day, riboflavin at 15 and 20 mg/day, and niacin at 40, 60 and 100 mg/day). Since dose–response studies were not conducted and the outcomes varied in the studies, it is difficult to make a specific recommendation.

However, all doses of the B vitamins studied were safe and effective in delaying progression of HIV disease.



Plate 6. Posted Divine Fermented (Encapsulated) Blood Tonic Supplement for HIV Infected Patients

c. Vitamin c

Vitamin C, also known as Ascorbic Acid (AA), is a water-soluble antioxidant necessary for normal tissue growth and repair in the body. Since the body is unable to manufacture AA, it must be incorporated in one's daily diet. AA is commonly found in a variety of fruits and vegetables. It is an essential antioxidant for enhancing superoxide anion and hydroxyl radical scavenging, and boosting immune response. AA has been shown to prevent LPO damage to OS-induced cells. There has not been much study with AA and its role in treating HIV-infected individuals. While one report revealed sustained high dosages of vitamin C to be toxic and immunosuppressive to T-cells, physiologically sustainable dosages may be beneficial for warding off the adverse effects of ROS and improving immune response at the time of infection. Future studies monitoring both AA dosage and duration are essential in elucidating its role in HIV infection.

d. Vitamin E

Vitamin E is a lipid-soluble vitamin. Its antioxidant properties are involved in protecting vitamin A and essential fatty acids from oxidation, thereby preventing the breakdown of tissues. Similarly to vitamin C, humans cannot generate vitamin E; thus, it must be supplemented into a daily diet from corn, lentils, wheat, rice or nuts. Vitamin E is a family of eight isomers; α -tocopherol is the only form that is actively maintained in the human body and found in the largest quantities in the blood and tissues, specifically in cell membranes. Vitamin E deficiencies and OS have been associated with HIV-seropositive patients [60]. A study of 296 HIV-infected men showed a decrease in the risk of progression of AIDS by doubling their vitamin E intake.

In addition, while AZT remains one of the primary medications used to reduce viral levels of HIV-1, it has been shown to cause bone marrow toxicity. It was found that a concentration of 1 to 100 micromol/L were able to significantly increase the growth of bone cells in culture. This suggests that combination therapy of AZT and vitamin E may have the similar anti-viral effects, while suppressing

bone marrow toxicity.

Vitamin E supplementation has also been found to reduce NF- κ B levels in HIV-1 infected lymphocyte cell cultures and lower oxidant production in lymphocytes, thereby reducing viral replication and inhibiting cell death. Vitamin E has been suggested to have a protective role in cell membranes by preventing LPO due to its lipophilic nature, as well as elevating the activity of other antioxidants to aid in the scavenging of free radicals [64]. One study revealed that vitamin E acetate completely blocked NF- κ B activation in HIV-1-infected cell cultures, while vitamin E had a minimal effect. Additional studies are needed to confirm this report of a different redox form of Vitamin E having promising results, as well as in determining therapeutic values of the time dependence and proper dosages essential for potential clinical application.

2.24 Minerals

a. Iron

During infections, iron is sequestered from plasma into storage depots and is not used for synthesis of hemoglobin. Over time this may result in anemia. Anemia is a common condition in HIV infection and a prognostic marker of future disease progression or death, independent of CD4⁺ T-cell count and viral load. However, anemia in HIV infection is usually multifactorial, including deficiency of protein, vitamins A, E, B₁₂, folic acid and zinc or a combination of them, as well as a consequence of bone marrow suppression by the HIV virus or other infections such as malaria, neoplasms, blood loss and medications. Low hemoglobin levels in HIV-infected patients are also associated with enhanced cellular immune activation, evidenced by increased IFN- γ , neopterin and β 2-microglobulin, and with changes in iron metabolism. Thus, endogenous release of cytokines may be another underlying cause of anemia in HIV infection.

The low hemoglobin observed in HIV infection may, paradoxically, be associated with high plasma ferritin levels, as well as iron accumulation in bone marrow, liver, macrophages, and brain and muscles cells. Elevated serum ferritin levels have been associated with more frequent infections and shorter survival times in patients with HIV infection in an observational study. In reticulocytopenia, common in HIV-associated anemia, endogenous erythropoietin is low, and a blunted erythropoietin feedback mechanism may contribute substantially to the relatively high prevalence of anemia in HIV-infected patients. However, iron deficiency is a common cause of anemia in HIV infection, particularly in women in inner cities whose nutrient intakes have been found to be inadequate, and in children from sub-Saharan and East Africa where the prevalence of HIV infection coincides with high prevalence of malnutrition and iron deficiency. In iron deficiency anemia, supplementation is needed to reverse the deficiency, and adequate dietary intake of iron through the course of the disease and treatment is critical to prevent the condition.



Plate 7. Posted Kuciana Hotel in Obudu Where the Researcher Lodge

Apart from the socioeconomic factors that may interfere with adequate iron intake, an observational study in HIV infection prior to ART suggested that HIV infection causes anemia by hindering absorption and metabolism of iron due to damage to the gastrointestinal system by opportunistic infections or the virus itself, impaired hematopoietic processes and intractable diarrhea that may occur in AIDS.

The treatment of severe anemia in HIV-1-infected patients is critical, as recovery from anemia has been associated with increased length of survival in these patients. Oral or parenteral therapy for anemia in iron deficient HIV-infected children has resulted in an improved production of hemoglobin. Calis *et al.* conducted a meta-analysis of 36 studies on anemia in children with HIV infection. The investigators compared and analyzed studies in developed and resource-poor countries and concluded that anemia is significantly more prevalent in HIV-infected than in non-HIV-seronegative children, and, as with adults, failure of erythropoiesis was the most frequent mechanism for anemia in HIV-infected children. In patients with anemia unrelated to iron deficiency, blood transfusions and iron supplementation to treat HIV-related anemia, however, may activate HIV expression and facilitate disease progression in patients not on ART and without controlled viral load. These observations are also supported by *in vitro* studies, which indicate that iron-mediated oxidative stress is likely to contribute to viral cytopathogenicity. Sappy and colleagues demonstrated that NF- κ B, a proviral transcription regulator, when activated by iron could enhance the production of reactive iron species involved in oxidative stress, which may play an important role in enhancing HIV disease progression. This is consistent with the findings of Delanghe and colleagues, who described abnormally high levels of HIV RNA in patients with haptoglobin 2-2, a less functional phenotype of the antioxidant protein haptoglobin, in an observational case-control study of HIV-infected patients who were not on ART. Those with haptoglobin 2-2 phenotype exhibited increased serum iron, higher transferrin saturation, lower vitamin C concentrations and increased serum ferritin compared with those with haptoglobin 2-1. The oxidant nature of iron and its potential depressing effect on the immune system makes treatment with erythropoietin preferable to iron supplementation for HIV-related anemia in patients who do not have clear evidence of iron deficiency.

Iron deficiency has been hypothesized to act synergistically with antiretroviral agents in inhibiting HIV-1

replication. In support of this hypothesis, an *in vitro* study demonstrated that iron-chelating agents, such as deferoxamine, inhibit proliferation of HIV-infected mononuclear blood cells. Iron-chelating agents render iron catalytically inactive, and enhance the action of some antiretroviral agents *in vitro*, using specimens from HIV-infected individuals. In addition, iron withdrawal from HIV-infected β -thalassemic subjects has been associated with protection against progression to AIDS. Additional evidence indicates that coadministration of low doses of oral iron and dapsone to prevent *Pneumocystis carinii jiroveci* pneumonia in HIV-infected patients was associated with excess mortality. These concerns have created a dilemma regarding the practice of supplementing iron for anemia in HIV-infected individuals who are not among the vulnerable groups for developing iron deficiency anemia. Although iron supplementation is the treatment of choice for iron deficiency anemia, in HIV infection, the risks of supplementation need to be weighed against the benefits. If there is a clear indication of iron deficiency using erythrocyte protoporphyrin, serum ferritin and transferrin saturation assays, iron should be supplemented. Low hemoglobin and hematocrit and low serum iron that may result from other nutrient deficiencies are not sufficient indicators of iron deficiency in HIV infection. Recombinant human erythropoietin therapy, frequently used for treatment of anemia in HIV infection, may be a more effective and safer means of improving hemoglobin than either blood transfusions or iron supplementation in patients with adequate stores of iron. Treating underlying infections, including HIV with ART, may assist in correcting some of the causes of anemia in adults as in children. In view of the evidence reviewed, iron intake, beyond the RDA levels for adults (between 8 and 18 mg/day) and pregnancy (27 mg/day), or the dose needed for treatment of iron deficiency anemia, are not recommended in HIV-infected patients.

b. Selenium

Selenium is the active component of the enzyme glutathione peroxidase in humans and may have a role in slowing down the growth of cancerous tumors. In animal models, selenium deficiency impairs the ability of phagocytic neutrophils and macrophages to destroy antigens. One of the mechanisms through which selenium status appears to influence humoral immune response is through its role in cytokine response. IL-2 is a Th-1 cytokine, responsible for the earliest and most rapid expansion of T lymphocytes. In *in vitro* models, selenium appears to regulate and enhance the production of IL-2 through the increased expansion of high-affinity cytokine receptors in a dose-dependent manner.



Plate 8. Posts the Already Finish Encapsulated Covid-19 Capsule

Selenium deficiency, prior to ART, has been shown to be predictive of HIV-related prognosis and survival, and deficient selenium maternal status, if not reversed, has been found to be associated with higher risk of intrapartum transmission, and fetal and child death. These findings have an important implication, since the prevalence of selenium deficiency ranges between 7 and 33% among various HIV-1-infected cohorts and increases as the disease advances to AIDS.

Observational studies in HIV-1-infected chronic drug users before the advent of ART indicated that selenium deficiency was an independent predictor of survival (RR: 10.8; 95% CI: 2.37–49.2; $p < 0.002$) in a multivariate model that controlled for the joint effects of nutritional deficiencies that had predicted mortality in univariate analyses. This significant effect of selenium was evident when controlling for a $CD4^+$ T-cell count of less than 200 cells/mm³ at baseline and $CD4^+$ T-cell count over time. When similar analyses were conducted in an observational study in a cohort of HIV-infected MSM and who were not receiving ART the odds ratio (OR) for mortality was 7.2 in those with low plasma selenium compared with those with normal selenium levels, after controlling for age, race and $CD4^+$ T-cell count below 200 cells/mm³ at baseline. In this cohort, selenium deficiency was also associated with decreased survival; patients with selenium deficiency lived for 31.4 months, compared with 57.4 months for those with normal plasma selenium levels after controlling for $CD4^+$ T-cell levels, viral load and antiretroviral medications.

In an observational study of HIV-1-infected children in the pre-ART era, selenium deficiency has been associated with immune dysfunction and decreased survival. Similar pediatric findings were reported from a 2-year study of 610 children born to HIV-infected women in Tanzania who were not on ART. The results of this observational study demonstrated that the children's plasma selenium levels were inversely associated with risk of mortality for all causes. Furthermore, low maternal plasma selenium levels were significantly predictive of risks of fetal death, child death and intrapartum HIV transmission, but were associated with lower risk of delivering a child small for gestational age.

The effect of selenium deficiency on HIV vaginal shedding has been mixed. Vaginal HIV shedding is considered a marker of risk of HIV transmission. In an observational study, selenium deficiency was associated with increased vaginal HIV RNA shedding in Kenyan women who were not on ART.

c. Zinc

Zinc is important for maintaining an intact immune system. Adequate levels of zinc are necessary for activation of lymphocytes. Zinc deficiency reduces generation of T cells, depresses humoral and cell-mediated immunity and causes lymphopenia, thymic atrophy, reduced capacity of macrophages to take up and kill parasites, and increased susceptibility to a greater number of infections. Many of these immune deficits generally correlate with the degree of zinc deficiency. Indirectly affecting and magnifying its impact on immunity, zinc deficiency also alters the membrane barrier permeability of endothelial and lung epithelial cells and causes ulcerations of the small intestine.

Zinc is essential for the function of the hormone thymulin, which is needed for the formation of T lymphocytes. In animals and humans, zinc deficiency results in a rapid and marked atrophy of the thymus, impaired cell-mediated cutaneous sensitivity and lymphopenia. Primary and secondary antibody responses are reduced in zinc deficiency, particularly for those that require T-cell production and the generation of splenic cytotoxic T cells after immunization. Zinc deficiency also increases production of glucocorticoids, inducing apoptosis of precursor lymphoid cells. However, studies in zinc-deficient mice demonstrated that while the lymphoid compartment is rapidly depleted, the myeloid compartment remains intact, sparing the first line of defense, the neutrophils and macrophages.

Zinc depletion studies in healthy volunteers have demonstrated that zinc deficiency influences the balance of Th-1 and Th-2 functions, and the expression of cytokines. In these studies, cytokines associated with the Th-1 subset of T-cell lymphocytes, IFN- γ and IL-2, were decreased, whereas those produced by Th-2 cells (IL-4, IL-6 and IL-10) were not affected. In addition, gene expression of IL-2 and IL-2 gene receptors, and binding of NF- κ B to DNA, were also decreased. Prasad hypothesized that decreased activation of NF- κ B and subsequent reduction in gene expression may cause the observed reduction in IL-2 [122]. Zinc supplementation resulted in a significant increase in IL-2 production and decreased incidence of documented bacteriological infections in mildly zinc deficient, but otherwise healthy persons. Zinc supplementation also inhibited production of TNF- α . Thus, at least one of the mechanisms through which zinc deficiency depresses some aspects of the immune response is by zinc deficiency promoting a shift from Th-1 to Th-2. It appears that supplementing zinc to zinc-deficient individuals increase the Th-1 type cytokines, thereby reversing this shift. In addition, zinc deficiency also reduced secretion of IL-4, resulting in significantly elevated levels of TNF, implicated in the pathophysiology of cachexia and wasting in AIDS. Zinc supplementation reduces morbidity in HIV-infected individuals, indicating an important role for adequate zinc status in reducing HIV-related opportunistic infections. Levels of zinc in ranges indicative of zinc deficiency are prevalent in HIV-infected male and female drug users, and are widespread in other HIV-1-infected cohorts. Such low levels of plasma zinc have been linked with faster HIV-1 disease progression, independent of baseline

CD4⁺ T-cell count, lymphocyte levels, age and calorie-adjusted dietary intake in the pre-ART era. In an observational study in a Miami cohort of 130 HIV seropositive MSM prior to the ART era, and who were followed for 4 years, those who became zinc deficient during the study had a mean CD4⁺ T-cell count decline of 111 cells/mm³, while those who increased their plasma zinc from the deficient to the adequate range had a significant mean increase of 61 cells/mm³ in CD4⁺ T-cell count ($p < 0.01$). The evidence shows that zinc doses above 15 mg were associated with adverse effects and are not recommended. In addition, HIV-infected populations who are zinc deficient, or at high risk of deficiency, in cohorts prior to ART or on ART, as well as patients on ART with controlled viral load, appear to benefit the most from long-term, low-level zinc supplementation.



Plate 9. Posted the Dry Granulated Herbal Medicine (HIV/Covid-19) into in Fine Powder in Readiness for Encapsulation

3. Methodological Approach

2. Methodology The standard procedure of identification, measurement and then evaluation of the costs was followed. K. Anand et al. / Health Policy 47 (1999) 195–205 197 2.1. Identification of costs HIV/AIDS has an impact on different aspects of economy. The costs included in the present study are the loss of productivity among HIV/AIDS patients both due to premature death and sickness, productivity loss due to caregiver of an AIDS patient, cost of management of HIV/AIDS patient, cost of strengthening blood banks. The costs not included in the present study are use of Anti-retroviral (AZT) therapy, cost of retraining of new unskilled workers, cost of strengthening of health system, cost of communication strategies, cost of research and development, cost of prevention of vertical transmission, and the intangible cost of pain and suffering to the patients and their families. All these methods were employ but there have not been prevailing success achieved except by the used of Divine fermented Naija Herbal therapy For HIV/AID cure currently in the year 2021



Plate 10. Posted the Researcher and the Packaging Materials

4. Literature Review Results and Discussion

4.1 Basic Strategy of HIV Virus Infect to the Host

Obviously, it is for mankind to draw him/her self and get acquainted to the way and manner killer virus HIV/AIDS operate in Human system. Thus, HIV replication cycle, which begins when HIV fuses with the surface of the host cell. A capsid containing the virus's genome and proteins then enters the cell. The shell of the capsid disintegrates and the HIV protein called reverse transcriptase transcribes the viral RNA into DNA. The viral DNA is transported across the nucleus, where the HIV protein integrase integrates the HIV DNA into the host's DNA. The host's normal transcription machinery transcribes HIV DNA into multiple copies of new HIV RNA. Some of this RNA becomes the genome of a new virus, while the cell uses other copies of the RNA to make new HIV proteins. The new viral RNA and HIV proteins move to the surface of the cell, where a new, immature HIV forms. Finally, the virus is released from the cell, and the HIV protein called protease cleaves newly synthesized polyproteins to create a mature infectious virus. As seen in Figure 1.

4.2 Clinica Survey and Share of Devine Fermented Natural Naija HIV/AIDS and Its Efficacy to so Many States, Local Government as well as Federal Capital Abuja, Phase 1

The lingering research project regarding to divine fermented natural Naija HIV/covid-19 project commence since 2019 has been a thing of do or die affairs within the reach of some communities. The most difficult part of the scenarios is when the researcher mentions HIV status, they almost and always ran mad regarding to the repugnant and agitating issues. Must men continue to hide under the canopy of devilish area of jurisdiction when the truth is revealed to them? As a matter of truth lies travel 100 times faster than the truth. Honestly speaking at one time the research was at the verge of given up the mantle after so many must have tested the strength and the efficacy of the divine fermented Naija natural HIV/ Covid-19 herbal drug/ vaccine therapy. Nonetheless the researcher has received so many reports on the issue that the herbal drugs/vaccine have no side effect irrespective of their ages. Lo and

behold it reaches to a particular point in time where by people would rather have taken it in secret mannerism after which it must have worked for them so efficiently. Thus, they would always asked for more as if it have become a habit. By and large the divine fermented Naija natural HIV/AID sherbal drug/vaccine therapy does not always take the recognition or care of HIV/AIDS status but also regarded to other ailments as seen in table 3. Most of the populace received the natural herbal drugs/vaccine over 50 persons have the highest followed by over 30 persons and the least were observed within over 15 and 12 persons within the country and outside. According to them it was a welcome development and highly recommended within the concern communities both in the local, state, national as well as outside the country. But why the registration of the herbal drug by NAFDAC is so lingering and repugnant; has there been a conspiracy going on against the microbiologist who has discovered the herbal natural therapy with the so-called medical doctor in the country? A prophet is not known in his country except at another country. In addition, the fermented divine Herbal medicine once taken and the illnesses gone, ones donot need to go and lick it vomits (SIN) or like the pig that is washed and warn never to go to back to gutter by the owner. Yet the pig would secretly find itself in the gutter i.e., habitual and deliberate sin ("Zunubin Gangachi" in Hausa). The researcher has been instructed for men ought to have been living a sinless life, for without holiness no human being would evercaught a glimpse of seeing the maker of earth and heaven home. Taking a brighter way of life to reaching many that were under siege in one way or the other in Cross River States local communities namely; Igalo, Ishibori, Obugu, as well as Ogoja, the researcher motive was to go for a burial funeral of a family friends i.e., in person of late Chief George Bengioshuye Agba. For this reason, he was the son of late major Abobo Agba (Retired). In the process of time as the researcher waspreparing for the burial funeral oflate Chief George Bengioshuye Agba, a though crosses there searcher mind for God assignment to humanity (Divine fermented Naiji natural HIV/covid 19 herbal therapy. There upon the researcher obeys God's command and carry go the natural herbal medicine to Cross river state namely Igalo, Ishibori, Obugu, as well as Ogoja communities. On arrival to Ogoja area of jurisdiction, the researcher lodge in the house of Ishibori headvillage namely Chief Kennedy for two days thereafter. On the other hand, the researcher who had come to Ogoja local government area with lots of joyful good news to the communities, has fallen a bit fear within him; for how he would have related to the head village of the issue of mankind toiling with lingering killer disease like that of HIV/AIDS status. Honestly at the very particular point in time the researcher wish it could have been diabetes, pile, Hepatitis, high blood pressure asthma ulceretc., respectively as seen in plate 2 trying to capture the man's heart so as he would have dance to the researcher's wishes. Going by the rules, it crosses the researchers mind to what must have given birth to such a multiple illness that men are habituated with. As a matter of truth, the genealogy of those ailments came from the master Killer HIV/AIDS as instructed by the maker of heaven and earth planet. Having discussed at length with the Head village of Ishibori as mentioned with these series of illnesses namely, diabetes, pile, Hepatitis, high blood pressure asthma ulceretc respectively. Thus, the researcher deliberately failed not to have let the cat out

of the bag to his knowledge, later the researcher decided to tell him where the geneses of these illnesses came from (it is not my mouth they would receive that the head of a village mess in the public). Suddenly the head village boasted into laughter and beg the researcher to please tell him. In a twinkling of an eye there searcher read his mind for he would not have taken an offense. For this reason, the researcher opens up by saying if the medical doctors/ scientists in the world would failed to have told mankind the truth about the killer disease then the common researcher would let it known to mankind. In Hausa language popular saying “Karya tana karewaammagaskiyabatakarewa”. It simply means lies have limit but truth has no limit. H.....I.....V/A.....I...D...S. The Head village mind was deeply read by the researcher of the truth the man was contemplating these things that have been in his body for long secretly and Dr. came and expose him within himself. Hmm.... History has repeated itself. Initially he thought the researcher only came for his in-law burial funeral, but the man came for to save his people lives. Having tested the efficacy of the divine fermented Naija natural HIV/AIDS at that very particular point in time, in side him he failed a dramatic change in the body after 15 minute or thereafter. He went straight and told his wife there is something their visitor gave him it appears so strength in comparison to the antiretroviral drugs he always takes. The wife asked him where is the drugs and he joyfully brought it out and shown her the miraculous drugs. Having does the wife has taken the miraculous drugs, her heart quickly jumped into her mouth with surprise by reporting to her husband like wise. The next following morning the common Dr. as the head village love to call the researcher Dr. my wife and I are feeling quite great and Olympic. Initially when the researcher saw them it appears as if they were not clinically sound but after that at 65 (Husband) or so and wife at 62 or so they were just feeling strong and Olympic. She quickly ran into kitchen for morning breakfast before she finally went to office (Primary school teacher). The next following morning he took the Dr. for a stroll within the local villages and to his sister whom the Dr/ researcher saw and he felt grief on her condition. Thereupon the researcher opens up for his physical and spiritual assignment, Chief this your sister has pile, diabetes, ulcer, high blood pressure but third one I wound not let the cat out of the bag for your hearing. The head village scream and shouted this man you are not ordinary. The researcher asked him to please give her the divine therapy for our God to be known. Having taken the natural drugs and next following morning she came to her brothers with full of joy. By and large there searcher felt he was sleeping too long in the village head bed; therefore, he asked the head village have they buried Chief George Bengioshuye Agba and how was their tradition regarding to burial funeral? He did tell the researcher that Late Chief George Bengioshuye Agba would be buried tomorrow and we shall be going there and sleep by the tomorrow everything would have been come to an end. From Ishiborito Ogoja is about 40 km or their after, having arrived at the Ojojavillage in some few minute then the corpse of Late Chief George Bengioshuye Agba was brough in the compound. There with the corpse was kept in a beautiful decorate modern hut over night before Late Chief George Bengioshuye was buried. The retired general Peter Abobo Agba saw me and felt so happy and called the researcher byhis father’s name Silas in Hausa” har ka samu ka so? He then pictures there searcher and found that

he was such a responsible person right when he had known the researcher at child hood. While thinking where the son of man would have laid his head for tonight before taken up to Kaduna. Suddenly a hillylock Bus came at the point of where the researcher would have slept along side with general who was the driver with a soldier on security came and took the researcher to a Hotel by name Kuciano hotel Obudu as seen in plate 3 and 7 the local champion has become an international champion. There is a significant difference between plate 3, 7 and plate 2. Well, if the Head village would have known he might have taken the researcher to a powerful hotel for him to enjoy with the babes around for that night. But the head village was just a retiree and pensioner for that matter and the difference was quite clear and no controversy in comparison with the retired general. While the general/his security on guard and the researcher were heading to the hotel for him to have rest, the researcher opens up his mission to him. The researcher mission was for his elder brother burial funeral as (primary issue) and the secondary issue was to save lives of the communities from the lingering killer disease that have been ravaging people's lives to their early grave. The products were produced in Kaduna polytechnic in the directorate of research and innovation. Thus, they were just natural herbal drugs and they are very effective. Therewith the researcher handed everything to him and we shall hear the feedback through the former Rector of Kaduna Poly now the Executive secretary of NBTE. The registered name would have been included but his phone number was not where to be found in my Handset. "Kai" see fine girls men..... in the hotel but I was afraid to touch any because of the HIV status. As instructed do not collect anything from anybody and so the researcher remain faithful to the instruction.

4.3 Spiritual/Physical Inspiration without it no Scientific Discoveries

As a matter of truth scientists, lecturers, medical doctors etc., respectively have done quite well in keeping humanity in the right track. To be candid, let it be known to every respected profession. The spiritual happening is far much greater than the physical. When most researcher lives a sinless /holy life and follow the precept of the marker of heaven and earth planet then they can visualize any tiny object be young the physical realm. Thus, life will go a long way and smoothly with mankind's. Scientist believed strongly in "seeing and believe" by physical means, but in some cases physical means objects are limited in comparison with spiritual means. Most illnesses in some cases can not be virtualize by the use of physical means material because they are limited. The spiritual always come in existence with everlasting promises while the physical with fake promises and limited in-situ. Most medical doctors and scientists are more prone to physical happening than the spiritual. Thus, when a patient case is far beyond human understanding using physical object, they normally referred him/her to spiritual professional for lasting solution or otherwise. The current researcher is more of a spiritual man than the physical or both. For this reason, most of the physical materials event that we are seeing these days must have happened in the spiritual before they manifest in the physical. For Instance, the inventor of plane does not start fly without an inspirational messages or sources. Likewise, the inventor of a car does not start moving with a car not until he/she has been inspired. Do the medical doctors start practicing his/her profession without an inspired word or source? In question, where do the sources of

the scientists, professional doctors, lecturers come from and which source? On a serious note, there is God source that led to unlimited wisdom while that of the devilish source is limited and leads one's to his/her early grave or destruction. Whosoever that sign evil covenant with the devil would always reap wrong results and reverse is the case with God. So much to say most scientists and the medical doctors/lecturers' sources of their profession come from wrong sources and that is why they never disclose to mankind the truth about the killer disease HIV/AIDS since 1981. To this effect they have even bought humanity into telling lies when they have been taken anti-retroviral drugs/ Artificial vaccine to their early grave. As instructed to let the humanity of the truth/ breaking news, who so ever that have that is another 2nd stage of the beast mark on his/her forehead (666). A word is enough for the wise.

4.4 Human Clinical Trials Using Divine Naija Fermented Herbal Therapy for (HIV/COVID-19) Infected Persons Phase II

By the Grace of God/Allah, the divine Naija herbal therapy was so designed and bestowed to the author so as men would have taken and lived longer than necessary as well as living blameless/ sinless life without qualm. The Divine herbal therapy was also given so as men would at- testified the finger of God Almighty of the natural herbal cure and not the suppressive types. Contrary wise, the research project had begun since 2019 with liquid and later graduated or transformed into syrup. Henceforth, the liquid and the syrup were however quite good by many people that have tested it, but there were some minor complains of the truth; if it's lasted for longer period of time in an ordinary temperature and not the freezing point it would have gotten spoiled by microbial spoilage. Only the Biochemists, Chemists, Micro-biologists, Biologist, chemical engineers as well as Physic too can ascertain what the author is trying to put across. If ones go to office for good 30 days without salary, would he/she have survived under the unfavorable condition? Similarly, to the microbes too the divine substrate is loaded with huge number of natural proteins both at the primary metabolites/secondary metabolites stages; hence, the net products are the production of microbial enzyme, vitamins, and so many, amino acid residues, vaccine, antibiotic, and isolates demand for organic synthetic that makes the huge number of natural proteins as seen in Table 2. At the secondary metabolites phase when the substrate has gone delated, then the rejuvenation not of but through phytochemicals comes up i.e., the fall of someone would have given birth to the rise of another person (anthraquinone, flavonoid, tannins, polyphenolic compounds, that target the HIV/ COVID-19 viral truck load as seen in the table 1 and 4. For the research done so far, for the Naija divine fermented herbal therapy, it was harvested at primary/Stationary phase. Point of correction as the suitable substrates or medium gone devastated by microbial spoilage at the death phase, the test and aroma or the net effect is an obnoxious odor like those of smelling dead rat inside the cardboard. In as much as the divine Naijaharvested herbal therapy is likening by most people at primary phase/stationary phase in-situ in plate1. So far, the product was then harvested at the required norm for sundry/ microbial ovum dryer in readiness for milling and encapsulation. As seen in plate 9. Please scientist or the lay men get the researcher right, at the point of primary stages (exponential

phase/stationary/fairly death phase most enzyme, vitamins, proteins in the plants species must have been converted to microbial enzyme metabolite and very rich in microbial enzyme proteins, vitamins, vaccine, amino acids antibiotic and photochemical strength at minimal concentration for virus/bacteria/ yeast/fungi likening. Thus, there is always an electrovalent attraction between enzyme active site + substrate and the antigen, unknown to the antigens (virus/bacteria/yeast/fungi etc. respectively in the medium (Blood) for their death warrant. Lo and behold the research project or work was like those of transitional phases, starting from ground stage (Stationary) to excited stage (dynamic/encapsulation stage). In addition, further research work will be circumspectly and assiduously be carried out in-readiness for tablet formation and so on later induce cause. For this reason, Rome/USA/India were not built in a day. Oh..... No..... can something good come out of Nigeria? Oh..... it's impossible by the white men but it possible with God/Allah. More so most of the Divine Naija samples products were always channeled to NAFDAC for ascertaining the efficacies whether there are traces of toxicity and there was none what so ever. As a matter of truth none of the result were made available for the reach of the researcher for further amendment so as many would at- testified for the job well done (Turn their deaf ears on the researcher products, but use it). To be candid there was no products of the Divine Naija Herbal therapy products that would not be channeled to NAFDAC for ascertain whether it is nontoxic or toxic after a successful project. Thus, for the truth to be on pipe line, they do enjoy the sweet smelling fermented and the healing therapy of divine Naija fermented herbal therapy for HIV as well as Covid-19 for the betterment of their lives. In addition, they also wish the formula would have been given to them so as the government would have known NAFDAC have gotten an herbal therapy for HIV/Covid-19 cure within their areas of jurisdictions. More often many of their staff have tested the researcher's products produce in Kaduna polytechnic with ease. For this reason and Knowing fully of the truth they always, felt very great, contented and quite Olympic as the information always hit the researcher's ears for joy. The researcher also formulated the production of Blood tonic and multivitamins as seen in plate 6 and 5 as instructed/directed and by what the virus/bacteria /fungi wants from literature review search and were channel to NAFDAC for confirmation once again. Lo and behold the natural Protein synthesis is by far much greater than the conventional ones during the test in NAFDAC Lab. All of a sudden, the technicians/analysts heart melted like candle wax before the fire. Wonderful and incredible! Further investigations were made by the researcher and it appears as if the researcher has little or no idea on the algorithm of research project in-situ. Thus, it also looks as if the researcher is like those local hawkers that sale herbal therapy without scientific standard/norm (Dr. Mainasara/Madaran Ayu). Since the results of the researcher's findings were not always given to the author, for further correction in line with the very much populace that have tested the divine fermented herbal capsules therapy in-situ. Nonetheless out of the delayed from NAFDAC which could be very dangerous to many lives as the HIV/covid-19 novel is ravaging people lives, as directed by I'm that I'm (God) *God appeared to Moses in the **burning bush** and told him to go to Egypt to lead the Israelites out of slavery. In response, Moses said to God, "Suppose I go to the Israelites and say to them, 'The*

God of your fathers has sent me to you,' and they ask me, 'What is his name?' Then what shall I tell them?" God said to Moses, "I AM WHO I AM. This is what you are to say to the Israelites: 'I AM has sent me to you'" (Exodus 3:14-15). As instructed, sent the first wave/batch of the therapy to your beloved senior lecturers(all are professors now in FUT Minna/FUTY YOLA Adamawa where the researcher bagasse his 1st and 2nd degree for the test of God finger regarding to Divine Naija fermented herbal therapy. Furthermore, the researcher was instructed to send a token to IITA Ibadan, British/American tobacco company Ibadan, Kano state, Jigawa State, Katsina State, and some part of Southern Kaduna Kachia, Zonkwa, and Madakiya. Some token to KASUPDA, Kaduna State University, Kaduna State Immigration department officers, some part of Kaduna environ, American Embassy in Abuja, German Embassy in Abuja, Biotech Center too at Abuja, British/ England through my in-law Biuadded, etc. respectively as see in Table 4. As a matter of truth all those who might have tested the therapy are feeling very much great, reliable, stronger than ever and quite Olympic or 100% OK! Most of them were even looking forward to when the 2nd or 3rd batch of God finger therapy will be sent to them. To be candid upon the touring the researcher has made so far, no single Kobo what so ever that was collected from them as God instructed. More so apart from the HIV/COVID-19 Cure, other ailment regarding to bacteria/fungi disease were gone from the hundreds and thousands of people that have tested it. For instant the report some people always come to tell the researcher is that HIV is gone, Covid-19 is gone fibroid gone, Pile, gone, liver symptom is gone, diabetes gone, cough is gone, pneumonia is gone, arthritis is gone, blood pressure is gone etc. respectively. Lo and behold a Muslim woman (IBIRA) whom the researcher saw her and he felt a bit upset, and the researcher promise her the Divine God finger in-situ. As the divine fermented herbal therapy was administered to her after 3 days, she came to Kaduna polytechnic looking for the researcher calling Doctor of all doctors. Suddenly he rebukes her for that names, for it is a curse to be answering such Medical terms Doctor "Likitan-likitochi" in Hausa/ Dr. Mainasara/Dr Mama Aisha/Academic Doctor but rather than research Dr simple. She offered the researcher some money and he rejected, for it is out of God rules and regulations at that particular point in time. The Researcher have realized that for as many are HIV carrier, they are always afraid to be mention HIV carriers and when the divine fermented therapy is given to them, and has gone completely. Thus, they would always have fallen into temptation (Fornicate) for another HIV. Sin is always sweet to the canal minded people. Is just like when one wash a pig and told the pig not to go inside the dirty water/gutter for play, however in one's, absence it will secretly find itself suck inside the gutter. That is what they called deliberate sin of fornication. To that effect. that is how the carnal minded people toil with sin of fornication until he/she visits his/her early grave with so many illness/ so many signs and symptoms. As a matter of truth as instructed the researcher lingering findings by NAFDAC was as a sign of conspiracies that was going on between, he NAFDAC Head and the Minister of Health couple with some doctors. Is the researcher a medical doctor? No, is a common microbiologist. Who wants to bear that name medical doctor when there is no element of truth in research program found circulating among the Nigeria medical group of doctor area

of jurisdictions? Furthermore, the researcher is not Dr Abalaka whom they crucified as per then, even though he was not fully grounded in the algorithm of research findings. Thus, they rule out the divine Naija fermented herbal therapy for artificial Covid-19 made up of chemical synthesis with numerous side effect age wise. A prophet is not known in his country except at another country But Jesus, said unto them, A prophet is not without honor, but in his own country, and among his own kin, and in his own house (Mark 6: 4). For their selfish and satanic interest for people to be dying with (Covid-19) infected patients' carrier at all cause for money. What shall it profit a man if he gains the whole world and loses his/her live in *Hell* ^{For} ***what shall it profit a man, if he shall gain the whole world, and lose his own soul? (Mark 8:26).*** when one is at 60 and above, that he/she is quarter to carry go the coffin inside grave, then what is man justification toward making heaven?

Note: Nigerian mentally they don't appreciate what their fellow brother does but preferred to enrich another man's country. Naira Value have gone depreciation in comparison with Dollar due to perpetual over dependent on imported chemical recipes that have ravaged so many people live to negativism or early grave (HIV stated ever since 1981). How can Africa grow so as to beginning to eat the fruit of her labor from the student they've home base train using her locally available endogenous materials? My in-law by namely David Orchonogor tested the efficacy of the divine fermented Naija natural products HIV/Covid-19 and his mouth directly jumped into his heart with surprises. He even took some to England for trials, as matter of truth the multivitamin booter and blood tonic superseded their own. He gave them theherbal medicine to some white men and it was a shook to them. Questioning where does this wonderful and miraculous medicine came? He did tell his in-law from Nigeria. Can anything good come from Nigeria. They told they needed the therapy hotly they wouldn't mind what so ever it might cause them they will pay. My in-law never discloses the matter with me and buried it within himself and wife my sister. Was I there? But God told me. Your enemy cannot come from the South, North, West, East but it is your brother and extended family that crucified one.

4.5 God Warning to Adulterated People of Generation of Grace (End Time)/Biblical Facts

The Biblical facts of why God allowed the children of Israelite to be punished by their neighboring countries that did not fellowship him as demanded. Thus, it was as results of the following sins (**Boko haram, Kidnapping, Banditry, Abortion, Fornication, homosexual, gay married, pedophilic dubious attitude, adultery, idolater (visiting the iniquities of our fore fathers) bestiality**, etc., respectively. Thus, Sodom and Gomorrah under the leadership of prophet Abraham were seriously punished after series of intercessors right from 50 to 2 persons; hence, there was no righteous one except his nephew Lots. Even lots his brother was not qualified but it was by God grace he spear the life of prophet Abraham's nephew. On D-day of God's wrath upon humanity there was heavy cried for mercy under the torment of fire like volcanoes, hot Furnace like those sulfur and methane as seen in Figure 21.



Figure 6. Posted the Wrath of God Is Being Revealed from Heaven Against All the Godlessness and Wickedness of People, Who Suppress the Truth by Their Wickedness Roman 1:18

However, the same episode was employed to that Prophet Noah due to the above-mentioned forbidding sins. Lo and behold for the wrath Of God to be fold on his creatures, there are always series of warning like those of pestilence, earthquake, famines, wars, volcanoes eruptions from different magnitude so as to scare mankind from being victim of circumstances. The same episode was applicable to the generation of Noah, when God selected him to warn humanity from being a partaker of the above mention highlighted forbidding sins. Lo and behold mankind's have adamantly turned their deaf ear to God servant and eventually the wrath of God be fold upon them through water flood for their total destruction. Only Noah and his children that were safe alongside with animals both male and female for a new generation to continue as seen in Figure 2 2



Figure 7. Posted Noah His Family and Animal Were Save for Continuity of a New Generation

(Genesis 6:1-13). It was as a result of the above mention highlighted forbidding sin that God sent Prophet Jonah to the people of Nineveh so as to warn them to desist or shun themselves into such dubious acts. Thus, prophet Jonah though that God did not see him and he assiduously, meticulously

and secretly wanted to escape God instructions to another location. Unfortunately, the ship Jonah boarded was found shaken by strong storm that let the people inside the ship to have thrown him inside the sea after admitting his fault. Thus, Jonah was swallowed by a whale and have been in the whale belly for good consecutive 3 days, and after he was vomited by the whale at the bank of the river. Suddenly Prophet Jonah Worship God and went straight for the errand. However, they don't tell person train is coming or otherwise. Thereupon when the message of God through prophet Jonah touches their heart (People of Nineveh) so they repented and eventually the wrath of God went into the air without hurting them. As seen in Figure 23.



Figure 8. Posted Prophet Jonah Was Thrown Inside the Sea Simple Because he Fails to Deliver God's Message to the People of Nineveh Currently Assyria Country Due Their Terrible Atrocities (Deliberate sin of Adultery, Fornication, Abortion), etc. Respectively

JONAH FLEES FROM THE LORD

1 The word of the LORD came to Jonah son of Amittai:² "Go to the great city of Nineveh and preach against it, because its wickedness has come up before me." But Jonah ran away from the LORD and headed for Tarshish. He went down to Joppa, where he found a ship bound for that port. After paying the fare, he went aboard and sailed for Tarshish to flee from the LORD. Then the LORD sent a great wind on the sea, and such a violent storm arose that the ship threatened to break up.⁵ All the sailors were afraid and each cried out to his own god. And they threw the cargo into the sea to lighten the ship. But Jonah had gone below deck, where he lay down and fell into a deep sleep.⁶ The captain went to him and said, "How can you sleep? Get up and call on your god! Maybe he will take notice of us so that we will not perish." Then the sailors said to each other, "Come, let us cast lots to find out who is responsible for this calamity." They cast lots and the lot fell on Jonah.⁸ So they asked him, "Tell us, who is responsible for making all this trouble for us? What kind of work do you do? Where do you come from? What is your country? From what people are you?" He answered, "I am a Hebrew and I worship the LORD, the God of heaven, who made the sea and the dry land." This terrified them and they

asked, “What have you done?” (They knew he was running away from the LORD, because he had already told them so. The sea was getting rougher and rougher. So they asked him, “What should we do to you to make the sea calm down for us?” “Pick me up and throw me into the sea,” he replied, “and it will become calm. I know that it is my fault that this great storm has come upon you. Instead, the men did their best to row back to land. But they could not, for the sea grew even wilder than before. Then they cried out to the LORD, “Please, LORD, do not let us die for taking this man’s life. Do not hold us accountable for killing an innocent man, for you, LORD, have done as you pleased.”¹⁵ Then they took Jonah and threw him overboard, and the raging sea grew calm. At this the men greatly feared the LORD, and they offered a sacrifice to the LORD and made vows to him. Now the LORD provided a huge fish to swallow Jonah, and Jonah was in the belly of the fish three days and three nights. Jonah1: 1-15. As seen in Figure 23.

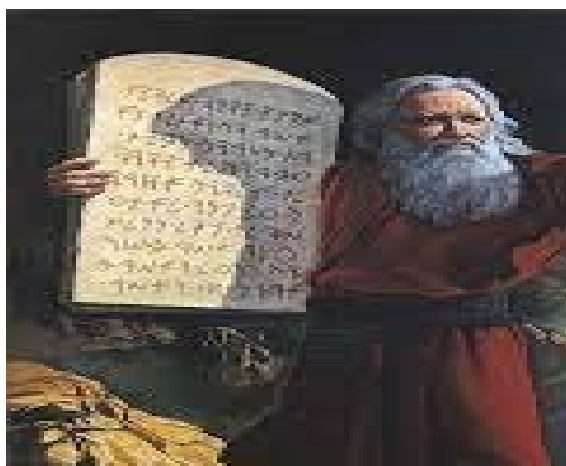


Figure 9. Posted Moses and the Ten Commandments

At the generation of grace, i.e., this generation everyone seems to be toiling or playing with sins at his/her own will when God Almighty has laid down principle for men to immolate his precepts/commandments through his written hand as seen in fig. 23 *I am the Lord thy God! Thou shalt have no other Gods but me! Thou shalt not take the Name of the Lord thy God in vain! Thou shalt keep the Sabbath Day holy! Thou shalt honor father and mother! Thou shalt not kill! Thou shalt not commit adultery! Thou shalt not steal! Thou shalt not bear false witness against thy neighbor! Do not let thyself lust after thy neighbor’s wife! Thou shalt not covet thy neighbor’s house, nor his farm, nor his cattle, nor anything that is his! (Exodus 20:1-17)*

So many plagues/wars have come and gone by ravaging people lives to their early grave as a result of the above highlighted mention sin of forbidding by God; yet people have not learnt from the past mistakes or change their habits of leaving Holy. On the other hands the introduction of Homosexual and gay married is another abominable sin that will rather trigger the wrath of God upon mankind’s. By and large just a tip of an ice bag was found be folding to mankind since 1981 (HIV) pandemic and up

to now there is no cure; except, Suppressions through Antiretroviral therapy/ Higher active Antiretroviral therapy. Another noble pandemic Covid -19 is around the corner ravaging people live to their early grave and scientist have claimed they have gotten the vaccine when it is not. This will continue to be like HIV pandemic when HIV carrier patents are under (ART/HAART) made of up synthetic chemicals ingredients with many lingering side effects. For these reason God is sending strong warning messages to mankind's to shun deliberate sin of fornication, sin of abortion, sin of homosexual, sin of having sex with small children (Pedophilic), sin of Gay married, another sin in Hausa language "Dan daudu" is more or less have sex man to man, Bestiality (Sex with animals or animal having sex with man). This sound warning is on everyone, least God will one day destroy humanity with methane, Sulphur and volcanoes fire as hot as furnace. Let those who have ear to read the article to change for the better, for only those whose are found of fallen into pang of frustrating and disappointing God's precepts on earth planet will be destroy. Thus, the good ones will be taken to heaven and the earth will remain as it is for another generation to continue the race.

Fig 24 The biblical account of Sodom and Gomorrah is recorded in Genesis chapters 18-19. Genesis chapter 18 records the Lord and two angels coming to speak with Abraham. The Lord informed Abraham that "the outcry against Sodom and Gomorrah is so great and their sin so grievous" (**Genesis 18:20**). Verses 22-33 record Abraham pleading with the Lord to have mercy on Sodom and Gomorrah because Abraham's nephew, **Lot**, and his family lived in Sodom. They called to Lot, 'Where are the men who came to you tonight? Bring them out to us so that we can have sex with them'" (**Genesis 19:4-5**). The angels then proceed to blind all the men of Sodom and Gomorrah and urge Lot and his family to flee from the cities to escape the wrath that God was about to deliver. Lot and his family flee the city, and then "the LORD rained down burning sulfur on Sodom and Gomorrah — from the LORD out of the heavens. Thus he overthrew those cities and the entire plain, including all those living in the cities..." (**Genesis 19:24**).

In light of the passage, the most common response to the question "What was the sin of Sodom and Gomorrah?" is that it was **homosexuality**/gay, rapping, abortion, fornication bestiality, pedophilic dubious activities etc., respectively . That is how the term "**sodomy**" came to be used to refer to anal sex between two men, whether consensual or forced. Clearly, homosexuality was part of why God destroyed the two cities. The men of Sodom and Gomorrah wanted to perform homosexual gang rape on the two angels (who were disguised as men). At the same time, it is not biblical to say that homosexuality was the exclusive reason why God destroyed Sodom and Gomorrah. The cities of Sodom and Gomorrah were definitely not exclusive in terms of the sins in which they indulged.

4.6 Conclusions

Once the first incident of HIV infection was reported in 1981, its implications and symptoms brought much concern to clinicians and researchers. Its global spread presented a serious problem. The subsequent opportunistic diseases from infection and slow progression to AIDS were alarming. Novel advances in diagnosis and treatment brought much hope to researchers. They believed that if it were

possible to catch the infection at an early stage and the agents that led to its life-threatening consequences, treatment might alter the course of these agents and save lives. However, as most virologists had known, this would be no simple task.

ROS were found to play a critical role in accelerating and controlling the progression to AIDS. In addition, antioxidant depletion was found to be a common sign at the onset of HIV infection, which resulted in severe OS. This imbalance gave way to pro-oxidants that activated replication and transcription pathways of the virus. Therefore, it was thought that antioxidant supplementation might suppress the effects of OS and slow the progression to AIDS. Although several reports are optimistic in their therapeutic use for HIV infection, further studies are essential to verify these results. Limitations remain with regards to the stage of infection, proper antioxidant dosage and duration, and resistance to treatment. Randomized trials utilizing appropriate dosages of antioxidant(s) are essential in investigating their role in altering the course of HIV infection.

4.7 Expert Commentary

HIV/AIDS has developed into a global problem that shows no sign of ceasing any time soon. Several studies indicate new advances in diagnosing and treating the infection, yet almost all remain costly. Antioxidants offer a promising, natural, and inexpensive remedy that may not only alter the course of HIV infection to AIDS, but also prove invaluable in reaching out to poverty-stricken countries.

4.8 Five-Year Review

There has been extensive study in the pathogenesis of HIV/AIDS over the past few years. An overwhelming number of treatment studies focus on the use of protease inhibitors and antiretroviral agents rather than antioxidants. However, a majority of these reports face tremendous difficulty due to the ever-mutating HIV strains. Although the mutations have no effect on the virus, the genetic flexibility permits drug resistance and the virus to escape the body's immune system.

A majority of research has focused on the use of highly active antiretroviral therapy (HAART) to suppress HIV viral replication and the progression of HIV disease. The hope is that daily treatment will stop any further Attenuating of the immune system, and thus, allow it to recover from any injury already caused. Reports have revealed HAART regimens that have successfully controlled AIDS and its related disorders, as well as reduced the amount of active virus to undetectable levels at times.

However, recent studies have indicated a rise in prevalence of HIV-1-associated neurocognitive disorders and related side effects following the era of HAART. An *in vitro* study investigated whether HAART drug combination of AZT and Indinavir (IDV) may alter the Blood-Brain Barrier (BBB) endothelial cells, which may exacerbate this condition. Following 72 hours of treatment, the viability of the cells was significantly reduced in a dose-dependent manner and levels of ROS were highly elevated. AZT+IDV treatment also induced apoptosis in endothelial cells. Interestingly, pretreatment with NAC reversed some of the pro-oxidant effects of AZT+IDV. The authors suggested that this AZT+IDV combination treatment might affect the BBB in HIV-infected individuals treated with HAART drugs.

An additional study investigated the related side Effects of Efavirenz (EFV), which is another widely

used treatment for HIV-1 infection. Similar to previously discussed study, viability was reduced in a concentration-dependent manner and EFV triggered apoptosis. EFV also lowered cellular proliferation and directly affected mitochondrial function in a reversible fashion by decreasing mitochondrial membrane potential and increasing superoxide production. As previously demonstrated, this study found the toxic effect of EFV treatment to be partially reversed by antioxidant pretreatment.

The elevated levels of ROS in each study indicate HAART generates ROS, thereby provoking the onset of OS, which has already been well established to occur upon HIV infection. Hence, while the oxygen faces a paradox, so does HAART: although viral loads may be suppressed, it is at the expense of elevated ROS levels that are known to only activate HIV transcription pathways and promote cell death. Therefore, since NAC treatment has been demonstrated to suppress some of the pro-oxidant effects of antiretroviral treatment, antioxidants in combination with HAART may reverse neurocognitive disorders and additional opportunistic infections associated with HIV-1 infection, while still working to reduce viral loads. Since a substantial amount of evidence reveals a role of ROS in inducing OS following HIV infection, and OS as a causative factor in the progression of many diseases, including AIDS, a turn of focus should be put on antioxidants as natural and inexpensive therapeutic agents to suppress the consequently life-threatening disease. Future studies should be undertaken to determine the correct dosages and duration of antioxidant treatment necessary to curb the adverse effects of HIV infection. Furthermore, comparative studies may serve to identify co-factors that contribute to the development of AIDS. With a better understanding of the co-factors that assist in progressing the disease, there is tremendous hope of improved diagnosis and treatment to perhaps alter the course of HIV infection and prevent the onset of AIDS.

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