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Research Article

Antiretroviral Therapy Resistance and Patient's Response to HIV-1 Allied Genotypes' patterns in Sudan. Pattern of Opportunistic Infections Among HIV-1 in Sudan

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Abstract

Introduction: Human Immunodeficiency Virus-1 (HIV-1) becomes a threat concern in the recent years in Sudan, many subtypes developed resistance against most common antiretroviral especially in co-infections with *Mycobacterium tuberculosis* drugs rifampicin.

Objectives: to determine Antiretroviral Therapy Resistance and patterns of opportunistic infection among HIV patients.

Methods: Collected samples were implemented using routine surveillance to utilize as the HIV diagnostic. Two hundred positive HIV patients tested by ELISA and (RT-PCR) sequencing for HIV resistance genotyping using dried plasma spot. Virus load was used to monitor the course of disease and the response to antiretroviral therapy in patients. T-cell count test gives an indication of the number of CD_4 cells in a person's bloodstream. The HIV-1 pol region from the viral clones of index patients, source patients in the same geographical area and wild-type HIV-1 subtype's strains were aligned to confirm the linkage between sources and index viruses, the sequence alignments were generated using Clustal W 1.6. The intra-variability percentage of each viral population, pairwise evolutionary distances were estimated using Kimura's two-parameter and maximum likelihood methods. The trees were then constructed using the neighbour-joining method.

Results: Around 90.9% cases were found to be HIV-1 positive and 9.1% were negative. The distribution of HIV-1 subtypes in North Sudan (A and C) (1.0%), in East Sudan (A, C and D) (8%, 9% and 3%), in West Sudan (3%, 7% and 2%) and in Center Sudan (19%, 6% and 3%). In South Sudan State (A, C and D) (15%, 10% and 13%) respectively. Patients responding to antiretroviral therapy was 71% and those non-responding was 29%. The opportunistic infection found among patients' were (36%) Fungal infection, Viral infection, Tuberculosis, other Bacterial infections (32%). HIV- 1 subtypes among intravenous drug users was (2%) subtype (A), (3%) subtype (C) and Non IDU subtype was (44%) subtype (A), (30%). HIV-1 subtype and Opportunistic infection were viral infection (12%) subtype (A), (8%) were subtype (C) subtype (D). Tuberculosis (12%)subtype (A), (16%) subtype (C) and (4%) subtype (D). Other bacterial infections (1%) subtype (A). According to our results, we found that, there was no significant association between HIV-1 subtypes and opportunistic infection, $P > 0.05$, The different clinic with subtypes were dermatology, surgery and psychiatry clinic the common subtypes found on the patients were subtype (A), (C), and (D), we found that the more common subtype was subtype (A). The study showed no significant association between HIV-1 subtypes and patient's attending different clinics $P > 0.05$, Moreover, we found that there was no significant association between subtypes and marital status $P > 0.05$. Never- the less, there was no as-

sociation between Blood transfusion as mode of transmission – and HIV-1 subtypes $P > 0.05$. The confirmed HIV-1 positive patients given the antiretroviral drugs named triomune after three months of treatment, the CD_4 count was re-estimated as indication and monitoring for Antiretroviral drugs response and resistance.

Conclusion: Determining the antiretroviral therapy resistance and opportunistic infection with HIV characterization is very important for clinical decision to obtain more facts about the virus polymorphisms, mutation, ARVs resistance and to determine the circulatory recombinant Forms(CRFs). Determination of the association between HIV Tuberculosis patients treated with ARV and Rifampicin is a key role in building our policy and strategy for HIV treatment and vaccination.

Keywords: *Antiretroviral; Genotypes; Opportunistic infection; Resistance; Sudan*

Introduction and Literature Review

Resistance of HIV to antiretroviral drugs is one of the most common causes for therapeutic failure in people infected with HIV. Standard antiretroviral therapy (ART) consists of the combination of at least three antiretroviral (ARV) drugs to maximally suppress the HIV virus and stop the progression of HIV disease. There is increasing data on subtype-specific variations in susceptibility to antiretroviral drugs, with some well-documented differences in the resistance mutational patterns to specific drugs according to subtype [1]. A relationship between genetic subtype and natural resistance against antiretroviral drugs has been reported. The development of drug resistance limits treatment options, facilitates viral rebound, and ultimately leads to immunologic decline and the development of opportunistic infections [2]. A current area of some controversy is the association of emerging mutations with viral subtype. For instance, preferential emergence of the K65R mutation has been described in subtype C-infected patients failing stavudine/didanosine-based regimens in Botswana [3]. HIV is a rapidly replicating virus that has error-prone reverse transcription giving rise to mutations throughout its genome, the enzyme, reverse transcriptase (RT) that transcribes viral RNA into DNA, introduces random mistakes during the process of replication leading to the development of new circulating strains and variants in a single individual. Sub-optimal concentrations of antiretroviral drugs in blood or tissues favour the selection of viruses harbouring mutations conferring resistance to the circulating drugs. The drug resistant strain will dominate and continue to replicate irrespective of the presence of the therapeutic agent. Suboptimal concentrations of the drug can be the result of poor adherence, drug quality, and bioavailability or drug interactions. The result is virologic failure and rising VL which eventually causes declines in CD4 counts and clinical progression [4]. The drug-drug interaction between rifamycin antibiotics (rifampin, rifabutin, and rifapentine) and four classes of antiretroviral drugs: protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTI), CCR5-receptor antagonists, and integrase inhibitors were reported [5]. Only two of the currently available antiretroviral drug classes, the nucleoside/nucleotide analogues (NRTI) with the exception of zidovudine [6,7] and the entry inhibitor enfuvirtide (given parenterally) [8], and are free of clinically significant interactions with the rifamycins. Although serum concentrations of the NRTI zidovudine are diminished by co-administration of rifamycins, no dose adjustment is recommended as the relationship between zidovudine plasma concentrations and efficacy is unclear. Interactions between drugs can favour the selection of HIV drug resistance by reducing the concentration of antiretroviral drugs to suboptimal levels. MDR, for example, has been shown to reduce the levels of nevirapine between 20% and 58% and efavirenz by 26% [9,10]. Patients with advanced HIV disease (CD4 cell count < 100 cells/mm3) have an increased risk of acquired rifamycin resistance if treated with a rifamycin-containing regimen administered once-, twice-, or thrice-weekly, especially during the intensive phase (first 2 months) of therapy, when bacillary load is still quite high [11-12]. Tuberculosis drugs, especially rifamycins, should be administered 5 to 7 days per week for at least the first 2 months of treatment to patients with advanced HIV disease [13]. In addition, populations exposed to antiretroviral drugs before initiation first-line antiretroviral therapy are also more likely to carry pretreatment resistance [14], leading to more rapid virological failure and further acquisition of HIV drug resistance [15,16]. Most interactions between HIV and TB therapy are through induction or inhibition of metabolic enzymes in the liver and intestine. The most important family of enzymes is CYP450. The CYP3A4 isoform metabolizes many drugs, including PIs and NNRTIs. Rifamycins are potent inducers of CYP3A4 and have clinically important interactions with PIs and NNRTIs. Of all medicines, MDR is the most powerful inducer of CYP3A4

[17,18]. MDR also increases activity of the intestinal drug transporter PgP which contributes to the absorption, distribution and elimination of PIs. The enzyme-inducing effect of MDR takes at least 2 weeks to become maximal and persists for at least 2 weeks after MDR has been stopped. If antiretrovirals are started or changed at the end of TB treatment, this persistent effect on enzyme induction should be taken into consideration [19]. Rifamycins play a key role in the success of tuberculosis treatment. Therefore, despite the complexity of drug interactions between rifamycins and antiretrovirals, treatment of HIV-related tuberculosis requires their co-administration. This should not be avoided by using tuberculosis treatment regimens that do not include a rifamycin or by withholding antiretroviral therapy until completion of anti-tuberculosis therapy. In randomized trials, regimens without rifampin or in which rifampin was only used for the first two months of therapy resulted in higher rates of tuberculosis treatment failure and relapse [20,21].

Objectives

The Relation between subtypes and opportunistic infection, as well as the effect of antiretroviral drug on HIV/AIDS patients are also looked into and determine the effect of some antiretroviral drugs for those patients who are on treatment.

Better to remove failure to treatment and rifampicin science no data in the result. Thie result only concentrate on pattern of opportunistic infection.

Patients and Methods

Collection and transportation of samples

Samples were collected from the Central National Lab of the Military Hospital in Khartoum. Specimen collection can be implemented using routine surveillance methodology. Routine surveillance methodology attempts to utilize as far as possible the HIV diagnostic and clinical systems already in place and to utilize data and specimens collected for other purposes. The specimens were sent for HIV resistance genotyping y using dried plasma spot.

The HIV Drug Resistance Diagnostic system

HIV resistance genotyping is being implemented as a routine laboratory test by a diagnostic PCR based assays. In addition, the DNA sequencing equipment needed for HIV-1 drug resistance genotyping is highly specialised and used laser technology to detect the DNA fragments. A profile from a clinical sample, the quality of the final result was created. Computing support is required.

The Viral Load Test

Measurement of plasma HIV-1 RNA levels (virus load) can be used to monitor the course of disease and the response to antiretroviral therapy in patients with HIV-1-infection. Assays based on different methods for quantifying plasma HIV-1 RNA assay have been developed. Viral load tests provide an estimate of how much HIV is circulating in someone's blood. A viral load test measures the amount of HIV in a small amount (millilitre, or mL) of blood.

The CD_4 Count Test

This test, also known as a "T-cell count test," gives an indication of the number of CD_4 cells in a person's bloodstream. The more CD_4 cells a person has, the stronger their immune system is. A normal CD_4 count for someone without HIV is usually between 500 and 1,600. Experts generally agree that when someone's CD_4 count goes below 350, they're at a high risk for developing potentially dangerous illnesses. Common categories are such as following; Healthy 500 - 1,660, Borderline Low 350 - 500, Low 200 - 350, Extremely Dangerous 0 - 200.

Phylogenetic analyses

The HIV-1 pol region from the viral clones (1200 base pairs) of index patients, source patients in the same geographical area and wild-type HIV-1 subtype's strains were aligned to confirm the linkage between sources and index viruses. The sequence alignments were generated using Clustal W 1.6. To determine the intravariability percentage of each viral population, pairwise evolutionary distances were

estimated using Kimura's two-parameter and maximum likelihood methods. The trees were then constructed using the neighbour-joining method (neighbour program implemented in the Phylip package [22]). Internal node supports were verified using the bootstrap method with 100 replicates, and values above 95 were considered to support the linkage between source and index viruses. Precautions were taken to prevent transmission of sequence data implementation [23].

Results

Two hundred units of seropositive HIV patients, that tested by ELISA as reactive units, had their serum tested by molecular diagnosis to detect HIV-1 by using (RT-PCR) methodology. One hundred – eighty-eight most of the cases around 188 (90, 9%) were found to be HIV-1 positive samples, 12 (9,1%)cases were negative (-ve). The patient received from different disciplines such as skin and Dermatological clinic, medical clinics, surgical and psychiatric clinic was 3 patients. 87 (43.5%) cases, 88 (44.0%) cases 22 (11.0%) cases, 3 (1.5%) cases respectively Table 1.

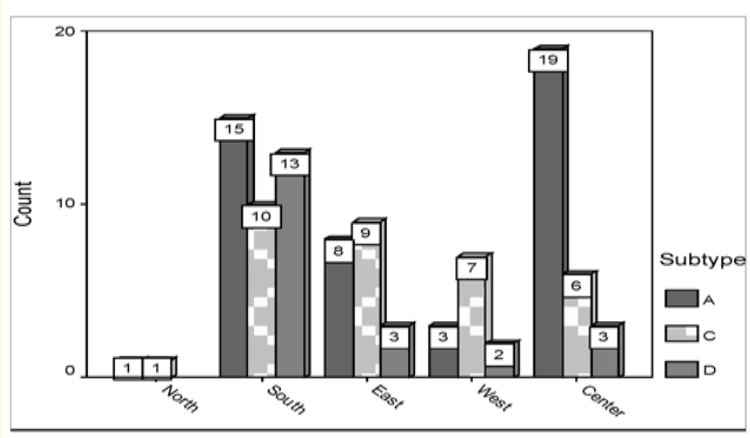

Figure 1: *HIV -1 Subtype (A), (C) and (D) distribution in Sudan.*

The distribution of HIV-1 subtypes according to the different areas was; in North Sudan subtypes (A) n = 1 (1.0%), subtype (C) n = 1 (1%). In South Sudan subtype (A) n = 15 (15%), subtype (C) n = 10 (10%) and n = 13 (13%) for subtype (D). In East Sudan subtype (A) n = 8 (8%), subtype (C) n = 9 (9%) and subtype (D) n = 3 (3%). In West Sudan subtype (A) n = 3 (3%) subtype (C) n = 7 (7%) and subtype (D) n = 2 (2%). In Center Sudan subtype (A) n = 19 (19%), subtypes (C) n = 6 (6%) and subtype (D) was n = 3 (3%).

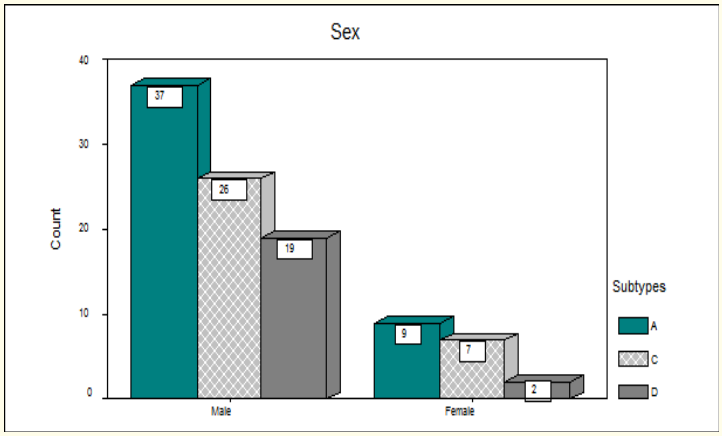

Figure 2: *HIV -1 Subtypes distribution among sex.*

The overall distribution of HIV-1 genotypes (A, C and D) among gender in the various subpopulations of interest.

	Frequency	Percent
Skin	87	43.5
Medicine	88	44.0
Surgery	22	11.0
Psych	3	1.5
Total	200	100.0

Table 1: *Distribution of HIV among different clinics.*

The opportunistic infection found among patients' were seventy two (36%) Fungal infection, Viral infection, Tuberculosis, other Bacterial infections sixty Four (32%). Sixty-one (30%), and three patients were 72 (36%) cases, 64 (32%)cases, 61 (30.5%) cases and 3 (1.5%) cases respectively (Table 2).

	Frequency	Percent
Fungal	72	36.0
Viral	64	32.0
TB	61	30.5
Bacterial	3	1.5
Total	200	100.0

Table 2: *Distribution of HIV among Opportunistic Infection.*

HIV- 1 subtypes among intravenous drug users was 2 pts (2%) subtype (A), 3 pts (3%) subtype (C) and Non IDU subtype was 44 pts (44%) subtype (A), (30%) subtHIV-1 subtype and Opportunistic infection were viral infection 12 pts (12%) subtype (A), 8 pts (8%) were subtype (C) subtype (D). T.B. 12 patient (12%)subtype (A), 16 pts (16%) subtype (C) and 4 patient (4%) subtype (D). Bacterial;1 patient (1%) subtype (A) (Table 3).

			Subtypes			Total
			A	C	D	
Infection	Viral	Count	12	8	9	29
		% of Total	12.0%	8.0%	9.0%	29.0%
	Fungal	Count	21	9	8	38
		% of Total	21.0%	9.0%	8.0%	38.0%
	TB	Count	12	16	4	32
		% of Total	12.0%	16.0%	4.0%	32.0%
	Bacterial	Count	1	0	0	1
		% of Total	1.0%	.0%	.0%	1.0%
Total		Count	46	33	21	100
		% of Total	46.0%	33.0%	21.0%	100.0%

Table 3: *Distribution of HIV-1 Subtypes among opportunistic infection.*

Other Bacterial infections were subtype (A). According to our results, we found that, there was no significant association between HIV-1 subtypes and opportunistic infection, P = 0.170. The different clinic with subtypes were dermatology clinic the common subtypes found on the patients were subtype (A), (C), and (D). Medical clinic subtype (A), (C) and (D). Surgery subtypes (A), (C) and (D). Psychiatry subtypes (C), we found that the more common subtype was subtype (A). The study showed that, there was no significant association between HIV-1 subtypes and patient's attending different P = 0.302 of significance, Moreover, we found that there was no significant association between subtypes and marital status P = 0.211. Nevertheless, there was no association between Blood transfusion as mode of transmission – and HIV-1 subtypes, P = 0.595.

The confirmed HIV-1 positive patients CD_4 count were estimated before given the antiretroviral drugs named triomune which was a triple therapy of the combination of lamivudine, stavudine and Nevirapine. After three months of treatment, the CD_4 count was re-estimated which was an indicated and monitoring for Antiretroviral drugs response and resistance.

Anti – retroviral Therapy and resistance

Currently available drugs belong to 4 therapeutic classes: reverse transcriptase nucleoside or nucleotide inhibitors (RTNI) non – nucleoscriptase reverse transcriptase inhibitors (nNRTI).

Class	Name	Brand	Laboratory
RTNI	Abacavir(ABC)	Ziagen Videx®	GSK
	Didanosine (dd1)	Emtriva® Epivir®	BMS
	Emtricitabine (FTC)	Zerit® viread® Hivid®	Gilead
	Lamivudine (3TC)	Retrovir®	GSK
	Stavudine (D4t)	Combivir®	BMS
	Tenofovir (TDF)	Trizivir®	Gilead
	Zalcitabine (ddC)		Roche
	Zidovudine (ZDV or AZT)		GSK
	AZT + 3TC		GSK
	AZT + 3TC + ABC		GSK
nNRTI	Delavirdine (DLV)	Rescriptor®	GSK
	Efavirenz (EFV)	reyatez®	BMS
	Névirapine (NVP)	Viramune®	GSK
PI	Amprénavir (APV)	Agenerse® Reyataz® Tel-	GSK
	Atazanvir (ATV)	zir® Crixivan® Viracept®	BMS
	Fosampénvir (fosAPV)	NoRvir® Forovase®	GSK
	Indinavir (IDV)	Tipranavir® Kaletra®	MSD
	Nelfinavir (NFV)		Roche
	Ritonavir (RTV)		Abbott
	Saquinavir (SQV)		Roche
	Tipranvir (TPV)		Boehringer
	Lopinavir (LPV)+RTV		Abbott
FI	Enfuvirtide (T20)	Fuzeon®	Roche

Viral load usually becomes undetectable after 3 to 6 months. Effective antiretroviral treatment also leads to a gradual increase in CD_4 Lymphocyte levels. In the event that viral loads reappears or increases to over 1000 copies/ml, a control using a new sample is advisable to confirm viral escape. Viral escape may be due to poor compliance with the treatment regimen, metabolic problems or the selection of resistant mutants.

Discussion

In the distribution of different subtypes in different areas of Sudan, we found that subtypes (A) and (D) were common in south of Sudan. This means that the patients most likely get their infection from the bordering countries with the same subtypes, such as, Uganda, Kenya, and Zaire. The common subtype in center of Sudan was subtype (A) then subtype (C) and subtype (D). These results may reflect the nature of the capital of Sudan represented by many population from different areas with different social behaviors. The distribution of HIV-1 subtypes among patients with different opportunistic infection were viral infection with subtype (A), (C) and (D), Fungal infection with subtype (A), (C) and (D) TB, (A), (C) and (D). Most of the patients are heterosexual, their clinical profile mainly medical, dermatological, surgical and psychiatric with 44%, and 43.5%. 11% and 1.5 % respectively (infection in most of the cases). Fungal infection, viral, TB and bacterial account for 36%, 32. 30.5% and 1.5% respectively (table 2). Medical problems like diarrheal and loss of weight (as reflected by visit to medical clinic) account in 44% of the patient (table 1). Al of 200 patient no history of homosexual, so all are due to heterosexual which is in consistency of other international study [24] (table 1). The clinical presentations indicate signs and symptoms of infection with medical and surgical clinic visit. The of clinical profile of HIV 1 in the paper agree with Lucknow by Ayyagari., *et al*. Amritsar by Aruna Aggarwal., *et al* [25,26]. Our present study showed infection due to TB to account for 30.5 of our patient which is in agreement of other worldwide studies [25,26]. TB prevalence among HIV patient in our studies is also falling with WHO data [27-29] Fungal infection in our work is account for 36% of the cases with accordance with Baradkar., *et al* [30,31]. Infection regarding in gastrointestinal tract are very common in our patient which agree with some Indian and other world countries [32-34]. Automated sequencing offers the most complete data on viral genotype, but generates more information than is needed for most clinical purposes. For example, HIV-1 RT has 550 amino acids, but mutations at only a small number of these positions are implicated in drug resistance. The study showed that the commonest subtypes that responded to antiretroviral drugs were subtype (A) and (D), and according to the result I was found that the subtype (C) was more common on T.B patients and most of T.B patients are resistant to antiretroviral drugs. and Rifampicin therapy is considered a contraindication for treatment with this type of ART. I was agreed with the study of Dr. Issam Alkhidir and *et al*. in their result of detecting HIV-1 genetic subtypes in Sudan which were subtype C (30%) and subtype D (50%). (Hierholzer. M. Alkhidir, I. et al). Subtype C is similar to our result, but we were disagreed with them in the following that: the common subtype we were detected was subtype A and I believe that the commonest of subtype A is due to that, most of the patients were militaries, from areas bordering the high-risk countries which is common of subtype A. This work is similar to the study of Ann Atlas and et al. in Sweden, they said that: (The HIV patients of African origin showed that 77% of were responded ARV triple therapy) (35). This study is similar to our study even in the sample size for CD4 count which were 100 samples. Moreover, mutations that cause resistance to one drug might improve viral sensitivity to different drug (for example, the 184V mutation causes resistance to 3TC but sensitizes HIV-1 to AZT (36). Another potential disadvantage of genotyping is inter-laboratory variation. An international study compared the performance of laboratories on a blinded panel of samples containing wild-type or mutant viruses in different proportions (37). Resistance testing plays an important role in supporting therapeutic decision making. Genotype resistance testing is recommended in the event of therapeutic failure, such tests detect mutations that are known to confirm resistance to this drug, in the Reverse transcriptase (RTNI and nNRTI), protease (PI), or envelope (FI) genes.

Conclusion

Lastly, we conclude that: This is a first study and first attempt for determining Antiretroviral Therapy Resistance and HIV characterization regarding the results obtained it's only the opening step for starting researches in HIV to detect more facts about the virus polymorphisms, mutation, ARVs resistance and to determine the Circulatory Recombinant Forms(CRFs), that not detected in this study. Determination of the association between HIV Tuberculous patients treated with ARV and Rifampicin is a key role in building our policy and strategy for HIV treatment and vaccination, and I believe that we can reach our target.

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