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Review Article

HIV: A RAGING BEAST- CAN IT BE TAMED?

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ABSTRACT
As a catastrophe of serious medical and social significance, HIV/AIDS comes with dire consequences. The pandemic has been with us and is causing high mortality with no regard for age, race or societal status. Now into the third decade, we have seen advances in the treatment of infected persons yet, the pandemic rages on with millions of new infections occurring annually. The HIV vaccine has been elusive and quest for it disappointing and frustrating, prompting some to wonder if there will ever be an effective vaccine or not. A lot of information and campaigns is on about HIV prevention; leaving much to be desired in the areas of core HIV research, discoveries and other interventions. We have revealed some steps taken so far and where we stand at the moment.
KEYWORDS: HIV, vaccine, pandemic, raging beast

INTRODUCTION

The Human Immunodeficiency Virus is a lentivirus belonging to the family Retroviridae. The novelty and intrinsic importance of retroviruses have been underlined by the award of the prestigious Nobel Prize on no less than three separate occasions. Although initially controversial, was the iconoclastic proposal by Howard Temin that genetic information could flow "against the tide" from RNA to DNA, which was unequivocally confirmed by the subsequent independent discovery in 1970 by Temin and David Baltimore of the enzyme reverse transcriptase in retroviruses, for which they both shared the Nobel Prize in medicine and physiology in 1975. In 1981, HIV was discovered independently by Luc Montagnier an American and Francois Barre Sinoussi a Frenchman, both of who shared the Nobel Prize in 2008 with Harold Zur Hausen [1].

HIV exists in two immunological forms, HIV-1 and HIV-2. HIV-1 is divided into two phylogenetic groups: M (major) and O (outlier). Group M is further subdivided into subtypes A to K with two circulating recombinant forms AE and AG while HIV-2 is divided into subtypes A to E [2]. Although the first case of AIDS was described as recently as 1981, the pandemic has escalated at such a rate that by 1993 the World Health Organization estimated that over 13million young adults had been infected with HIV and over 2million already developed AIDS, most of whom had died [3]. The threat posed by AIDS has triggered an unprecedented effort by researchers and governments alike to understand and conquer this disease. Already, a lot is known about HIV than about any other virus of longer standing. Indeed, HIV now sets the pace in virus research. New concepts and techniques pioneered by HIV virologists are now being employed in every area of the discipline –from the regulation of viral replication, through molecular pathogenesis, to laboratory diagnostic methods and novel approaches in viral therapy and vaccinology [4].

ORIGIN OF HIV

The origin of HIV and AIDS has puzzled scientists ever since the illness first came to light in the early 1980s. The most recognized case of AIDS occurred in the USA in the early 1980s [5]. A number of gay men in New York and California suddenly began to develop rare opportunistic infections and cancers that were stubbornly resistant to any treatment. At this time, AIDS did not yet have the name but it quickly became obvious that all the men were suffering from a common syndrome [6]. The discovery of HIV was made soon after [7]. It is now generally accepted that HIV is a descendant of the Simian immunodeficiency virus because certain strains of SIVs bear close resemblance to HIV-1 and HIV-2, the two types of HIV [8]. In February 1999 a group of researchers from the University of Alabama announced they had found a type of SIVcpz that was identical to HIV-1. This strain was identified in a frozen sample taken from a captive member of the sub-group of chimpanzees known as Pan Troglodytes which were once common in West Africa [9]. Their final findings were published two years later in Nature magazine [10].

POSSIBILITY OF INTERSPECIES TRANSMISSION OF HIV

Many theories have been proffered for how HIV crossed from primates to humans. Firstly and most commonly accepted is the "hunter" theory. Retroviral transfer from primates to hunters is still occurring even today. In samples from 1099 individuals in Cameroun, it was discovered that 10 (1%) were infected with Simian Foamy Virus (SFV) an illness which like SIV was previously thought only to infect primates through butchering and consumption of monkey and ape meat. Discoveries such as this have led to calls for an outright ban on bushmeat hunting to prevent simian viruses being passed to humans [11].

Secondly some rather controversial theories have attributed it to being transferred iatrogenically (medical interventions) and that the oral polio vaccine played a role. In his book The River, Edward Hooper suggested that HIV could be traced to an oral polio vaccine called "chat" given to millions of people in Africa in the late 1950s which was grown in kidney cells of chimpanzees infected with SICcmz. This position has been criticized by many who feel that the oral administration of the vaccine is insufficient to cause HIV because SIV/HIV need to be directly introduced into the bloodstream to cause infection and that the lining of the mouth and throat generally

act as barriers [12]. In April 2001, the Wistar Institute in Philadelphia (one of the manufacturers of the chat) vaccine announced no trace of HIV in the vial of polio vaccines used in the programme [13]. A second analysis confirmed that only macaque monkeys kidney cells which cannot be infected with SIV or HIV was used to make chat [14].

Thirdly, the contaminated needle theory is an extension of the original "hunter" theory. In the 1990s, African health care professionals working on inoculation and other medical program were in the habit of using single syringes to inject multiple patients as they could not afford the huge quantities of syringes needed due to the cost. This would have transferred any viral particles within a hunter's blood from one person to another [15].

Fourthly, "the colonialism or Heart of Darkness" theory is one of the most recent to have entered into the debate. This is still on the "hunters" premise but explains how this original infection could have led to an epidemic. In the 19th and early 20th century, much of Africa was ruled by colonial forces. Their rule was harsh and in areas such as French Equatorial Africa and the Belgian Congo, many Africans were forced into labor camps where sanitation was poor, food was scarce and physical demands were extreme. These factors are sufficient to create poor state of health in anyone so that SIV could easily have infiltrated the labor force and mutated to HIV in a weakened immune system [16]. Also, it was believed that many laborers would have been inoculated with unsterile needles against diseases (to keep them alive and working) and that many camps actively employed prostitutes to keep their workers happy creating numerous possibilities for onward transmission [17].

Fifthly, is "the conspiracy" theory in which many believed was man-made. A recent survey carried out in the USA identified a significant number of African-Americans who believe HIV was manufactured as part of a biological warfare programme, designed to wipe out large numbers of black and homosexuals [18].

CROSS REACTIVITY BETWEEN HIV AND SIMIAN IMMUNODEFICIENCY VIRUS (SIV)

HIV-1 and HIV-2 are believed to be the result of cross-species transmission from Simian Immunodeficiency Virus (SIV) –infected chimpanzees and sooty mangabeys respectively, which represent two (SIVcpz and SIVsm) of the six major lentiviral phylogenetic lineages [19,20]. No evidence exists that SIV strains from the remaining nonhuman primate lineages have infected humans, although many grow in human cells invitro as do SIVcpz and SIVsm. Although SIV sequences were not identified in either case, the findings suggests that humans are probably exposed to different simian retroviruses that can establish new infections in humans. Nonhuman primates infected with SIV from the currently recognized lineages can harbor antibodies that serologically cross-react with some HIV-1 or HIV-2 antigens [21]. The potential exists for zoonotic transmission of diverse primate lentiviruses in many parts of sub-saharan Africa including the Congo River Basin [22]. This potential is supported by the identification of a Cameroonian man whose HIV serologic results were indeterminate but whose serum specimen reacted strongly and exclusively with an SIVmnd V_3 loop peptide [23]. An even more compelling case for cross-species is the recent finding of a Cameroonian man who may have been exposed to a colobus SIV, as indicated by a strong humoral (envIDR and V_3) and a weak cellular (gag) immune response [24]. In many cases, HIV western blots (WBs) with indeterminate profiles of SIV-infected monkeys resemble those of HIV enzyme immunoassay (EIA) -positive, WB – indeterminate human sera from Africa. In general, such indeterminate African sera from persons in the United States [25-27]. These data suggests that the WB –indeterminate patterns in HIV EIA –reactive sera from persons living in Africa may reflect more than just a recent HIV infection or an infection with a highly divergent HIV-1 strain; they may reflect either cross-reactivity with unknown pathogens of African origin or exposure to new HIV- or SIV- like strains [28].

FACTORS THAT LEAD TO THE SPREAD OF HIV

Reasons have been advanced for the spread of the virus among which are:-

Gender inequity and violence to women

In South Africa, women who have experienced physical or sexual intimate partner violence or are in relationships with low equality are at a greater risk of HIV infection compared with women who do not experience these situations. Also, men who have been physically violent toward partners are more likely to be infected with HIV [29]. Young women who have experienced sexual abuse in childhood are also at two-thirds greater risk of HIV infection [30].

Sex trade

In sub-Saharan Africa, India and many parts of the world, the HIV epidemic remains substantially driven by contacts with commercial sex workers [31].

Cultural practices

In developing countries, many are exposed to risky traditional practices such as scarification in which incisions are made. When this is done for many people without sterilization, the sharp objects used spreads HIV. Local manicurist and pedicurists use locally fabricated scissors and tools which make them culpable in the spread of HIV if not properly sterilized. Risky sexual behaviors such as indiscriminate sexual intercourse, high promiscuity without using protection also results in the infection. Groups at higher risk of infection are homosexuals, male and female prostitutes, injection drug users, blood transfusion recipients, children born to HIV infected mothers and heterosexual contacts of HIV infected individuals [2].

SEXUALLY TRANSMITTED CO-INFECTIONS AMONG HIV-INFECTED

Human Immunodeficiency Virus-infected victims are more likely infected with other sexually transmitted infections specifically syphilis and hepatitis B [32]. The incidence of herpes simplex virus-2 reduced by one-third following a change in the sexual behavior of men including less perpetration of intimate partner violence [33].

EFFECTS OF HIV-1 ON MALARIA INCIDENCE

HIV-1 infection increases the risk of and severity of malaria [34,35]. The best evidence for association between HIV-1 and clinical malaria comes from 2 longitudinal studies in Uganda where malaria transmission is of high intensity. A community-based study in rural Masaka found odds ratios of clinical malaria among HIV-positive adults compared to HIV- negative adults, of 1.2, 3.4 and 6.0 for CD_4 counts of ≥500µl, >200-499/µl and >200/µl respectively [36]. In Kinshasa, HIV-1 infection at any stage and clinically diagnosed AIDS increased malaria incidence by 1.2- and 2-fold respectively but the increases were not significant [37]. A birth cohort in Blantryre, Malawi found no HIV-related increase in the incidence of parasitemia [38]. In Kampala,

perinatally HIV-infected children with AIDS experienced notably fewer malaria episodes than HIV-infected children [39] which were attributed to increased use of chloroquine before hospitalization among the HIV-infected. In contrast, among children in Kinshasa from 1986 to 1988 who had received blood transfusions, those who were HIV-infected experienced 1.4 times more clinical malaria than those who were not [40]. The observed effect of HIV-1 on the incidence of clinical malaria may in part be the result of an increased incidence of recrudescence after the efficacy of anti-malarial treatment [41,42].

ABC OF HIV

Prevention programmes have focused on behaviour change since the early 1990s, using "ABC" as an acronym for protective behaviours: Abstinence, Be faithful, Condoms. Majority of programmes for young people promote abstinence and fidelity, with condoms as a fall-back option if sex happened. ABC has been criticised by many HIV prevention practitioners as being over-simplistic and a reason for limited success [43]. But the US Government saw a different set of weaknesses in the ABC method. They perceived that condoms were being promoted to young and old indiscriminately, to the detriment of abstinence and fidelity messages. This was thought to be disrespectful to the values of local faiths and traditions, particularly in relation to women. Also, evidence from the high prevalence, generalised epidemics in Uganda and Botswana in the 1990s seemed to show that the impact of condoms on the epidemic as compared to partner reduction and delayed sexual debut was limited. This was thought to be partly because people in regular partnerships were considered to be reluctant to use condoms, and because it was logistically difficult to ensure they were widely available to enable regular and consistent use [44]. There were also concerns that educating young people about condoms would reduce the effectiveness of the abstinence message and cause harm if condoms were then not consistently available [45].

Studies overwhelmingly demonstrate that condoms are highly effective in preventing HIV transmission. An evaluation of existing published evidence shows that correct and consistent use of male condom reduces the risk of HIV infection by at least 90%. All the evidence on condom promotion and distribution programmes indicates their efficacy at increasing condom use and decreasing the prevalence of HIV and STI. This makes condom promotion and distribution one of the most effective prevention programmes that exists [46]. Whilst it is true that we do not yet know enough about the complex role of condoms as a public health measure in high prevalence generalised epidemics, we know enough to say that they are an essential component of any HIV prevention programme. The female condom provides women with another type of condom for the prevention of pregnancy and STI/HIV, which they can use themselves. This is a key method for the empowerment of women and has also been shown to be effective in reducing the risk of HIV transmission [47].

GLOBAL RESPONSE TO HIV IN AFRICA

The WHO Global programme for the fight against AIDS was swiftly put into action and aimed to raise $1.5billion a year by the end of the decade to help prevention and educational efforts [48], with priority to Africa [49]. In 1996, UNAIDS was established to take responsibility for coordinating international action against the epidemic [50,51]. In 2000, after mounting pressure to make HIV/AIDS drugs more accessible to Africans, five pharmaceutical companies offered to negotiate steep reductions in the prices of the drugs for Africa and other poor regions [52]. At last it seemed that the world was sitting up and taking notice of the ravaging AIDS epidemic in Africa. The amount of money that western nations were willing to give to help scale-up treatment for those living with AIDS in Africa greatly increased in the new millennium. In 2001, the Global Fund to Fight AIDS, Tuberculosis and malaria was created [53-55] and two years later United States President George Bush announced the President's Emergency Plan for AIDS Relief (PEPFAR) [56]. Between 2001 and 2004, global funding for AIDS in low-middle income countries trebled to $6.1billion a year. UNAIDS estimated this to be 50% of all AIDS spending in sub-Saharan Africa during this period. In 2004–2006 the PEPFAR budget increased from $207 million to $322 million, which was to be spent in 15 countries, 12 of which are in sub-Saharan Africa, including Zambia. Fifty five percent of those funds are required to be spent on treatment and 10% on orphans and vulnerable children. Fifteen percent are recommended to be spent on palliative care for HIV+ people and 20% on prevention [57]. Prevention must cover blood safety, prevention of mother-to-child transmission, safe medical injections, AB activities and "other prevention". PEPFAR country teams are required to spend half of prevention funds on prevention of sexual transmission, two-thirds of which should be spent on AB (abstinence/faithfulness) activities [57].

Very recently, the United States Department of Health and Human Services in partnership with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) planned an investment of $130million over a five year period to transform African medical education and dramatically increasing the number of health care workers. Eleven programmatic awards each worth $10million, largely funded by PEPFAR will expand and enhance medical education and research training in the field of HIV/AIDS [58].

VACCINE STUDIES

Vaccines have been among the most effective public health interventions. Although a classic preventive vaccine remains the ultimate goal, the enormous genetic diversity and other unique features of the HIV envelope protein have thus thwarted attempts to identify an effective candidate. Based on studies of HIV pathogenesis in humans and animal models, vaccines that induce strong T-cell mediated immune responses even if infection is not completely prevented. Vaccine-induced T-cell responses may blunt initial viremia and prevent the early and massive destruction of memory CD_4^+ T cells that help control infection and prolong disease-free survival [59]. The initial empirical approach of immunizing with VaxGen's AIDSVax, a recombinant form of the outer glycoprotein -120(gp120) protein of the HIV envelope which was based on a strategy that was successful with hepatitis B virus, failed to protect volunteers from Infection, apparently because the vaccine did not induce broadly neutralizing antibodies [60].

Cytotoxic (CD_8^+) T lymphocytes, key effectors of cellular immunity recognize viral peptides bound to major-histocompatibility-complex (MHC) molecules on the surface of virus-infected cells [61]. They can kill or suppress cells infected with HIV in the laboratory [62], and the emergence of these lymphocytes correlates with early containment of viremia [63]. If natural-history and animal-model studies prove

to be predictive, people who receive T-cell vaccines before infection might remain disease-free for a prolonged period, and antiretroviral therapy which can be burdensome with serious side effects over time, might be delayed. Futhermore, if initial infection is blunted and memory CD_4^+ T cells in gut-associated lymphoid tissue are preserved, strong, vaccine-induced T-cell-mediated immune responses might draw down viral reservoirs by destroying HIV-infected cells before new viral particles are released [64].

CHALLEGES OF HIV VACCINES

A vaccine that conforms to the classic paradigm of viral vaccines remains the goal of efforts to develop an HIV vaccine. Such a vaccine would induce immune responses that prevent the establishment of HIV infection by clearing virus before latent viral reservoirs are produced. This goal may not be realized with first-generation vaccines. Futhermore, the window of opportunity for the immune system to clear the initial infection is narrow, since HIV integrates and establishes latent infection within days or weeks. This aspect of HIV infection puts it in sharp contrast with almost all other viral infections in which the initial rounds of viral replication do not establish a permanent reservoir of infection. For this reason, HIV poses greater challenge to the classic vaccination paradigm in which prevention of clinically relevant infection ultimately leads to the eradication of the microbe, even though initial rounds of viral replication may occur as a result, rational and empirical approaches to vaccine development have not been successful to date [59]. Secondly, enormous genetic diversity and mutations that occur with replication enable HIV to avoid immune surveillance [4]. Thirdly, conserved antibody targets on the outer envelope protein are hidden from immune recognition [65]. Basic research on the HIV envelope has since provided several clues in the effort to determine why induction of antibodies that neutralize primary isolates of HIV is difficult [66]. The envelope on the virion surface exists not as a monomer but as a trimer. Immunogenic regions of the monomer are occluded in the native trimer on the virion surface. The envelope protein is cloaked with numerous N-linked glycans, undergoes considerable conformational change on binding to the cell-surface CD4 receptor and exposes sequences that are highly variable [67,68]. The potential effect of antibodies directed against variable regions is negated by the emergence of these so-called escape variants [69,70]. This means that high levels of neutralizing antibodies may be required to prevent infection [71-73]. The implications of all these is that fundamental questions regarding HIV disease and the host response to the virus need to be answered. Also, fresh new ideas beyond the scope of classic vaccinology are urgently needed [59].

THERAPEUTIC INTERVENTION

In 2001, there were more than 20million people living with AIDS in sub-Saharan Africa, but only 8,000 people in the entire continent were accessing treatment [74]. Therefore, Kofi Anan opined that in the fight against HIV there was no us and them, no developed and developing countries, no rich and poor but only a common enemy that knows no frontiers and threatens all people [75]. The development of more than two dozen antiretroviral therapies to combat HIV infection has resulted in a dramatic decrease in morbidity and mortality in developed countries and, increasingly, in low- and middle-income countries as these therapies become more widely available [59]. Several national HIV treatment guidelines including the Nigeria guideline have recommended treatment with triple antiretroviral regimen when patients become symptomatic or have CD_4^+ <200µl of blood. The current development of antiretroviral therapy which includes new agents, new formulas and pharmacokinetics enhancements is directed to achieving better potency, higher genetic resistant barrier, less pill burden and once a day dosing. These will ultimately improve the adherence and long-term effectiveness of antiretroviral treatment [60].

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