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SeyedAhmad SeyedAlinaghi

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CONTENTS

FOREWORD

It is estimated that about 35 million people worldwide are currently living with HIV/AIDS and, fortunately, the number of AIDS deaths and new infections is also declining. The introduction of antiretroviral therapy for effective control and prevention has had a great role to play in reducing this infection. Further, age of HIV-infected patients have been markedly increased so that the issues related to *"HIV and aging"* are discussed in more details by many textbooks and articles. However, fundamental challenges still remain such as HIV stigma and discrimination, adherence to antiretroviral therapy, access to high-risk groups including homosexuals and vulnerable women, types of intervention and their effectiveness on high risk groups, as well as achieving commitment to agreed goals by countries.

A textbook may be required to address new developments on the HIV/AIDS from different aspects. The present book can be regarded as a useful resource on HIV for researchers, clinicians, and others dealing with HIV. It provides a review of hot topics in HIV/AIDS compiled by Iranian and foreign experts. Indeed, edited by Dr. SeyedAlinaghi, the book covers important basic, epidemiological and clinical research aspects and presents updated information to readers. It also refers to a number of new issues which have not been extensively studied.

We truly appreciate all the authors who help the editor by writing the book chapters, and hope to provide valuable information to readers and receive positive feedback for our work.

Alireza Yalda
Distinguished Professor
Tehran University of Medical Sciences
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PREFACE

The present book focus on hot topics in HIV/AIDS research and every chapter was prepared by experts in the field.

Despite a global decline in the number of new HIV infection, in some areas including the Middle East the incidence rate of HIV infection is increasing. Consequently, effective prevention strategies as well as increased access to antiretroviral therapy (ART) are needed. In fact, control efforts for HIV infection requires to achieve a 50 percent reduction of HIV transmission among people who are infected through injection drug use or sexual intercourse, and elimination of mother-to-child transmission by way of providing antiretroviral treatment to pregnant HIV-positive women with a coverage target of 90% by 2015. On the other hand, one of the main objectives of international organizations is to increase the access to ART both as a life saving medication for people living with HIV and as an effective practice to prevent the infection. Fortunately, the infection with HIV is not considered a fatal disease anymore and it turned into a chronic disease and HIV infected people may enjoy near-normal life expectancy and reach old age.

Unfortunately, HIV-related stigma and discrimination is still significant in most areas of the world. However, the integration of HIV services with Primary Health Care (PHC) has proved to be an effective measure put in place by some nations. Further, reforming current laws and regulations and the development of new anti-discrimination legislation seem to be important for effective preventive and treatment activities.

The current book does not cover all aspects of HIV/AIDS. But, it presents a brief account of major issues and developments dealing with basic, epidemiology and clinical research for medical and scientific applications in this field.

The editor appreciates the effort and patience of all authors who participated in the writing of the chapters.

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CHAPTER 1

Diversity and Global Epidemiology of HIV

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Abstract: HIV has probably originated from multiple zoonotic transmissions of Simian Immunodeficiency Virus (SIV) from non-human primates to humans in West and Central Africa. There are two HIV types: HIV type 1 (HIV-1) groups M, N, O and P and HIV type 2 (HIV-2) groups A–H. Within the HIV-1 group M, nine subtypes are found, designated by the letters A–D, F–H, J, and K. Within a subtype, changes in the amino acid sequence is observed in the range of 8-17%, but it can be as high as 30%, while differences between subtypes are generally found in the range of 17-35%.

In fact, when new combinations between different HIV-1 subtypes occurs, it results in different Unique Recombinant Forms (URFs), some developed into Circulating Recombinant Forms (CRFs) as propagated in three or more epidemiologically unlinked individuals. The viruses fueling these epidemics vary according to geographical regions, with clade C virus being the most prevalent worldwide, and clade B being currently the most prevalent in the United States and Europe.

Thirty years after the first description of AIDS, an estimated 35.0 million [33.2 million–37.2 million] people were living with HIV at the end of 2013. 2.1 million [1.9–2.4 million] had become newly contaminated with HIV in 2013, including 240000 children, and 1.5 million [1.4–1.7 million] HIV-infected persons died.

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Keywords: AIDS, CRF, Diversity, Epidemiology, HIV, Mutation, Recombination, Sequence, Subtype, URF.

1. INTRODUCTION

HIV has probably stemmed from multiple zoonotic transmissions of Simian Immunodeficiency Virus (SIV) from non-human primates to humans in West and Central Africa. Cross-species transmission appeared in the process of butchering and hunting of primates for capture and the bush meat, trade and custody of monkeys as pets [1]. More than 40 different non-human primate species harbor SIV infections, with each specie carrying a specie-specific virus [2, 3].

2. HIV GENETIC DIVERSITY

Several factors supply to the extraordinary high genetic heterogeneity of HIV-1: (a) error-prone viral DNA synthesis during reverse transcription, (b) high recombination frequencies accompanying reverse transcription, (c) the high levels of progeny virus production *in vivo*, and (d) large numbers of infected individuals [4, 5]. It has been estimated that within an HlV-1-infected person, viral genetic diversity increases by 1% every year from the founder viral strain during the early symptomatic phase of the infection [6].

There are various HIV types: HIV type 1 (HIV-1) groups M, N, O and P and HIV type 2 (HIV-2) groups A–H. The range of the epidemic caused by each group varies considerably. HIV-1 group M is liable for the global HIV pandemic (approximately 33 million contaminated individuals), group N has been found in a handful of people in Cameroon; while group O causes a few tens of thousands of infections in West–Central Africa and group P was recently identified in two individuals originating from Cameroon [7, 8]. HIV-1 groups M and N might have stem directly, but independently, from SIVcpz observed in the chimpanzee *pan troglodytes* in West–Central Africa [9, 10]. Conceivably, more HIV types in humans will be found in the future, as all HIV types may not yet have been discovered and new cross-species transmissions may happen in the future. In the HIV epidemics, the sequences of the different HIV-1 groups have further diversified in the populations, which have enhanced further classifications [3]. In the HIV-1 group M, nine subtypes are detected, selected by the letters A–D, F–H,

J, and K [11]. Within a subtype, variations at the amino acid level is in the range of 8–17%, but can be as high as 30%, while variations between subtypes are usually between 17-35% [3].

According to analyses on several genome regions and particularly full length genome sequencing, recombination is a substitution event between viral strains. Intra-subtype recombination was observed to be very general within group M subtype C [12]. In fact, recombination between different HIV-1 subtypes has developed different many Unique Recombinant Forms (URFs), several developed into Circulating Recombinant Forms (CRFs) as propagated in three or more epidemiologically unlinked individuals. To date, 68 different CRFs have been found [11]. Recombination of some CRFs with other subtypes or CRFs results in the so-called Second-Generation Recombinants (SGRs) [3].

Group O sequence shows a high diversity, leading to a classification of sequences into clades I–V and they are as genetically far-away from each other as group M subtypes. On the other hand, lower subtype-like signal in group O was obtained *versus* to group M because group O has not spread too a lot past its origin in West–Central Africa [13 - 15]. All group N viruses found in humans are narrowly associated, as the only two group P sequences reported [8].

3. GLOBAL DISTRIBUTION

In agreement with our increasing knowledge about the mechanisms of HIV transmission, this infection has decreased markedly over the past decade. The viruses fueling these epidemics vary according to geographical regions, with clade C virus being the most prevalent worldwide, and clade B being currently the most prevalent in the United States and Europe (Table **1**).

Table 1. Distribution of all HIV-1 sequences that have been included in the Los Alamos database [16].

Subtype	Number	Percentage
01_AE	28453	5.3%
02_AG	14826	2.8%
A	39389	7.4%
B	303348	56.8%

CHAPTER 2

HIV Transmission

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Abstract: The risk of HIV transmission varies widely by the type of exposure. Anal intercourse for both receptive and insertive partners has a higher risk *versus* vaginal intercourse, and vaginal intercourse is a higher risk act compared to oral intercourse. Also, receptive intercourse (both vaginal and anal) has an increased risk compared to insertive intercourse. Generally, the risk of HIV transmission for receptive anal intercourse, receptive vaginal intercourse and receptive oral intercourse is 0.5%, 0.1% and 0.01% per act, respectively. However, the risk varies widely depending on differences in factors such as co-occurrence with other sexually transmitted infections (STIs), level of viral load, stage of disease, and circumcision. Plasma viral load is considered as the strongest determinant of sexual transmission of HIV.

Higher rates of infection with HIV are exhibited among injection drug users mainly because of unsafe injecting behavior. The risk of HIV transmission per each drug injection is 0.67%.

Vertical transmission may occur during pregnancy by micro-transfusion of blood across the placenta; or during labor and delivery by the exposure of neonate with maternal blood and genital tract secretions, and after the birth through breastfeeding. It is estimated that 24-45% of HIV infected mothers transmit the virus to their offspring if there is no intervention. Maternal plasma viral load, co-infection with STIs, chorioamnionitis, concurrent HCV infection or active tuberculosis, and vaginal *versus* caesarean delivery are associated with the increased risk of vertical transmission. Contributing factors to mother to child transmission include breastfeeding pattern and duration, health status of maternal breast, and high plasma or breast milk viral load.

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SeyedAhmad SeyedAlinaghi (Ed.)

Keywords: Anal intercourse, HIV exposure, HIV sexual transmission, HIV transmission, HIV viral load, Mother to child HIV transmission, Oral intercourse, People who Inject Drugs, Risk of HIV transmission, Route of HIV transmission, Sexually Transmitted Infections, Vaginal intercourse, Vertical transmission.

1. INTRODUCTION

The HIV transmission risk varies widely by the type of exposure. Worldwide, the most common route of HIV transmission is sexual followed by drug injection and mother to child transmission [1]. The possibility of HIV acquisition varies for each type of exposure. Table **1** lists the risk of transmission for different exposures.

Some parameters may increase or decrease the risk of transmission. For example, receiving antiretroviral treatment can reduce the risk of HIV transmission from People Living with HIV (PLWH) to another by as much as 96% [2]. The use of condoms lowers the risk of HIV acquisition or transmission by about 80% [3]. On the other hand, concurrent Sexually Transmitted Infection (STIs) or a high viral load (usually in early and late-stage infection) can enhance the risk of HIV transmission. In the following sections, each three main route of transmission is discussed in more details.

Table 1. Estimated transmission risk of HIV per-act of different exposure type* [4].

Exposure route	Risk per 10,000 exposures to an infected source
Blood transfusion	9,000
Needle-sharing injection-drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse	1
Insertive oral intercourse	0.5

*Sexual risk of HIV transmission is estimated without condom use.

Recently reported study indicate that estimates for both receptive and insertive anal intercourse are greater than those reported in Table **1** (increased 1.8 and 0.7-fold, respectively); however, the former estimates fall within the updated CIs for these exposures. In this study, the projected per-act HIV transmission risk (all expressed as per 10000 exposures) took the highest value for blood transfusion 9250 (95% CI 8900–9610), followed by mother-to-child transmission 2255 (95% CI 1000–2990), receptive anal intercourse 138 (95% CI 102–186), needle-sharing injection drug use 63 (95% CI 41–92), and percutaneous needle stick injuries 23 (95% CI 0–46). Risk for other sexual exposures were 4 (95% CI 1–14) for insertive penile–vaginal intercourse, 8 (95% CI 6–11) for receptive penile–vaginal intercourse, and 11 (95% CI 4–28) for insertive anal intercourse. The risk of transmission for receptive and insertive oral sex is pretty low (95% CI 0-4) [5].

2. SEXUAL TRANSMISSION OF HIV

In most countries, HIV epidemic is driven sexually [1]. To HIV transmission risk quantification by each type of sex remains challenging. Ideal estimations would be result from prospective studies in serodiscordant partners for whom all sex acts and their context were recorded. But estimates often derived on longitudinal or cross-sectional research with population-based HIV prevalence estimates. Recall bias can happen in these retrospective studies. For more suitable estimations, important variables are often ignored, such as the HIV status of all sexual partners. Furthermore, people do not often engaged in only one type of sex to abstain from other types of sexual contact with a partner [5]. So concerning these restrictions, the estimates should be understood carefully [5].

Nevertheless, all studies have consistently presented that anal intercourse is a higher risk act *versus* to vaginal intercourse, which is a higher risk compared to oral intercourse. On the other hand the associated risk with receptive intercourse (both vaginal and anal) is higher compared to insertive intercourse [6, 7]. It should be noted that these estimations mainly derived from studies implemented before the availability of active antiretroviral therapy (ART) [7]. So these studies estimate the risk of HIV transmission from an untreated PLWH with unsuppressed average viral load [8].

CHAPTER 3

Mother-to-Child Transmission of HIV Infection: Timing, Risk Factors and Strategies for Prevention

Kenneth McIntosh*

Harvard Medical School, Harvard School of Public Health Emeritus Chief, Infectious Diseases Division, Boston Children's Hospital, USA

Abstract: Mother-to-child transmission of human immunodeficiency virus type 1 (HIV) occurs during gestation, during delivery, and during breast feeding. In an unprotected mother-child pair, transmission over-all occurs in 30-40%, with about one quarter of these transmissions *in utero*, one half during delivery, and one quarter during breast feeding. Most *in utero* transmission occurs in the third trimester. There are many risk factors for transmission, but the most important are the maternal viral load and the maternal CD4 concentration. Antiretroviral treatment of the mother has a potent preventive effect but must be administered throughout the risk period (that is, from early second trimester through the end of breast feeding). For *in utero* and intrapartum transmission, treatment probably acts through two mechanisms, namely pre-exposure prophylaxis in the fetus or newborn, and reduction in maternal viral load. Adequate voluntary counseling and testing for HIV and access to antiretroviral drugs are now critical preventive issues in this important mode of transmission.

Keywords: Antiretroviral therapy, Breast feeding, CD4 concentration, Delivery, HIV, Mother-to-child transmission, Pregnancy, Viral load.

1. INTRODUCTION

The realization that an acquired immunodeficiency might be passed from mother to child during pregnancy or at delivery came before the word AIDS had been

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coined, and before HIV had been discovered. In the early 1980's, in San Francisco, Newark, New York and Miami, pediatricians recognized infants were being born to women who used intravenous drugs (who by that time were known to be at risk of the newly described immunodeficiency then afflicting gays and drug users) or were the spouses of high-risk Haitian men, and that these infants were themselves developing a rapid-onset immunodeficiency, with severe opportunistic infections such as toxoplasmosis, pneumonia due to *Pneumocystis jirovecii* and refractory candidiasis, followed by premature death [1 - 4].

After HIV was discovered, the tests for antibody to it were made available, and methods were developed to grow it in culture, detect p24 in serum, and, finally, amplify its pro-viral or cDNA through Polymerase Chain Reaction (PCR). The picture of mother-to-child transmission of HIV was considerably clarified. It is the purpose of this chapter to review the information that has led us to our current concepts of mother-to-child transmission of HIV and the logic of our attempts to prevent it.

2. THE TIMING AND RISKS OF MOTHER-TO-CHILD HIV TRANSMISSION

2.1. HIV Transmission *In Utero*

Some of the earliest information on the timing of HIV transmission emerged from virologic studies of a second trimester abortus from a HIV-infected woman [5, 6]. Further studies from Baylor University in Houston indicated that pathologic examination of the products of conception from HIV-infected women who spontaneously aborted revealed widespread destruction of lymphoid tissue [7]. In this intriguing study, the products of conception from 14 pregnancies in HIV-infected women who spontaneously aborted throughout pregnancy (most in the 2nd or early 3rd trimester) were carefully examined. Seven of the 14 abortuses were HIV-infected with widespread destruction of the lymphatic system, indicating that the virus could be passed on to the fetus with lethal consequences in or before the 2nd trimester. Two early reports of induced abortions indicated frequent PCR positivity in fetal tissues obtained at 11-24 weeks' gestation [8, 9]. One study of 24 abortuses (one set of twins) timed from 11-24 weeks of gestation indicated that

30% had HIV nucleic acid detectable by PCR of various tissues (brain, liver, or lung), but only the one set of twins were positive by *in situ* hybridization [9]. No clinical information was presented in this publication (*i.e.* CD4 count, maternal clinical stage, maternal viral load). The other study found PCR positivity in all nine fetuses examined, but cultures and p24 assays were negative in all [8]. In this study all but a few mothers were asymptomatic at the time of the abortions. The PCR positivity rate in both studies is not compatible with subsequent information about the rate of *in utero* transmission in live-born infants (see below), so it seems likely that some contamination with maternal blood (despite attempts to avoid this) occurred, or that, for some other reason, PCR was picking up signals that did not indicate active infection of the fetus. Self-cure of the fetus cannot of course be ruled out but seems unlikely.

One important historical step in determining the timing and quantitative risk of vertical HIV transmission stemmed from the realization that the "sensitivity" of HIV culture and PCR in detecting the virus in infant blood was relatively low in samples obtained at birth in relation to samples taken at later times during the first year of life [10]. This observation was translated into a consensus definition of *in utero* infection (HIV culture or PCR positive in peripheral blood obtained at birth or within the first 48 hours) and intrapartum, or perinatal, infection (HIV culture or PCR negative on peripheral blood obtained during the first week of life, but positive later in a non-breast-fed infant) that became widely accepted [11]. Many studies from the U.S., Europe, Asia, and Africa then confirmed that the risk of infection *in utero* (without any intervention) was between 6 and 10%, and the risk of infection perinatally was about double that figure [12].

Quantitative information on the risk of infection during the various months of gestation has been, however, more difficult to determine. For example, the risk during the first trimester is unknown. The risk during the combined first and second trimesters, with survival of the fetus, is probably quite low, in the range of 1-2% or less. There is some information on this figure obtained from the trial of Lallemant and colleagues in Thailand that investigated the comparative efficacy of long maternal zidovudine (beginning at 28 weeks' gestation) *vs.* short (beginning at 36 weeks) [13]. Infection detectable in peripheral newborn blood at birth in those whose mothers received ZDV beginning at 28 weeks' gestation was

CHAPTER 4

Reducing Pre-partum and Intra-partum Transmission of HIV to Infants

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Abstract: The Acquired Immune Deficiency Syndrome (AIDS) is one of the major causes of deaths among women of reproductive age and a significant contributor to high infant mortality rates globally. Mother-to-child transmission occurs when HIV infection is transmitted from an HIV infected mother to her baby in pregnancy, labour, delivery and breastfeeding. Preventing Mother-to-Child Transmission (PMTCT) of HIV is critical to save lives and restrain the impact of the HIV epidemic. Mother-t--child transmission before, during and after delivery can be the result of HIV transmission in 30-35% of infants of HIV-positive infected mothers. In the past three decades, HIV screening and treatment for pregnant females as well as prophylaxis for perinatal HIV transmission prevention were developed. Because of prenatal HIV counselling and testing, antiretroviral prophylaxis, programmed caesarean sections and evading of breastfeeding, the amount of perinatal HIV transmission has significantly diminished in the world today. The World Health Organization's protocol recommends the increase of the eligibility of pregnant females with HIV infection to lifelong antiretroviral therapy when possible in order to achieve optimum health outcomes. The main missed opportunity in preventing perinatal HIV infection is a lack of prenatal care. Antenatal HIV counselling comprising testing of pregnant females is an efficient medical intervention that contributes to PMTCT of HIV.

Keywords: AIDS, Antiviral therapy, HIV, Mother-to-Child Transmission, PMTCT, Prenatal care, Prevention.

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1. INTRODUCTION

In 1983, the first cases of AIDS in infants were reported in America [1]. Because of new therapies and better understanding of HIV infection, perinatal infection rates have remarkably declined since 1983. Despite this decline, in 2004 there were still 138 infants born with HIV infection reported in the United States [2]. An infant born with HIV represents a missed opportunity, and commonly, more than one opportunity is missed during the care for the mother-infant pair. The Centers for Disease Control and Prevention (CDC) refers to these missed opportunities as the Perinatal Prevention Cascade [3]. Prevention opportunities can take place throughout a succession of stages and include:

- primary HIV prevention for women,
- prevention of accidental pregnancies in HIV positive females,
- improve ease of access to prenatal care,
- universal prenatal testing and counseling, and
- Antiretroviral (ARV) prophylaxis and treatment for all HIV positive pregnant females and their exposed newborns [3].

2. PREVENTING MOTHER TO CHILD TRANSMISSION (PMTCT)

Preventing Mother-to-Child Transmission (PMTCT) of HIV was first proposed as a global health policy in the late1990s [4], after the earlier diagnosis of HIV infected newborns. It has been reported that HIV transmission can decrease to 1-5% by using a possible prophylactic antiretroviral treatment. In the past three decades, HIV screening and treatment for pregnant females as well as prophylaxis for prevention of perinatal transmission have been developed considerably in United States and other developed countries [5]. This development has also improved HIV management across the world including the developing countries. In fact, treatment of HIV infection in pregnancy has increased with a rising number of women taking combination antiretroviral therapy or triple antiretroviral drug prophylaxis. With the worldwide prenatal HIV counselling and testing, antiretroviral prophylaxis, programmed caesarean sections, and evading of breastfeeding, the amount of perinatal HIV transmission has significantly declined to 2% in European countries as well as the United States [5].

In some regions of the world where effective combination regimens of antiretroviral drugs are accessible, the use of these regimens has resulted in a noticeable increase of survival of HIV infected individuals; and amounts of transmission of HIV from infected mothers to their infants has been diminished to as low as 1%. On the other hand, in poorly resourced settings and where effective combination of antiretroviral regimens are not easily accessible, the use of less intensive antiretroviral regimens has resulted in lesser but still remarkable decline in the number of HIV infant cases that contracted the infection through mother to child transmission [6, 7].

In recent years, the supply of antiretroviral drugs for the prevention of mother to child HIV transmission has grown rapidly in low and middle income countries. Consequently, numbers of HIV infected pregnant females receiving antiretroviral interventions have increased from 10% to 53% (2004 - 2009) [8]. Similar to any new drug, the emergence of the utilisation of antiretroviral drugs for HIV transmission in utero poses a challenge. While the evidence on birth defects and mitochondrial toxicity remains unclear, evidence has related protease inhibitors to preterm delivery, low birth weight and transient hematologic toxicities [9].

The World Health Organization (WHO, 2013) protocol recommends the expansion of the eligibility of HIV infected pregnant females to lifelong antiretroviral therapy when possible in order to achieve optimum health outcomes. Regardless of the CD4 count and the clinical stage (stage 3 or 4), this expansion would lead to an increase in the CD4 threshold. The increase in a CD4 count is indicative of good outcomes for HIV status. For females not requiring therapy for their own health, recommendations were made for them to receive ARV treatment to prevent HIV transmission to their infants during pregnancy [10].

According to the WHO reports, the prevention of HIV infection among infants needs four strategic approaches including:

1. Primary prevention of HIV infected patients;
2. Prevention of unplanned pregnancies in HIV infected females,
3. Prevention of transmission of HIV infection from mothers to children,
4. Providing ongoing support, care, and treatment to HIV infected females and

CHAPTER 5

HIV Infection and Cell Signaling Pathways

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Abstract: HIV infects cells of the immune system, particularly T CD4 helper cells. Interaction of viral proteins with the cell, modulate many signaling pathways in the immune system. This interaction facilitate to the HIV replication, trafficking and infection. The starting point in signaling pathways is the attachment of HIV envelope protein gp120 to the CD4 receptor and CCR5 or CXCR4 coreceptor. Such events result in calcium fluctuation and activation of various Protein Kinase C (PKC) isoforms. Moreover, it was reported that gp120 mediates chemotaxis and actin cytoskeleton rearrangement. After the integration of the provirus and gene expression, HIV regulatory and accessory proteins modulate the enzymatic activity of some of the protein kinases. Accessory proteins induction of G2 cell cycle arrest is found to reduce human immune functions through protection against T-cell clonal expansion that would optimize cellular environment for maximal viral replication. Also induced cell cycle arrest *via* a DNA damage-sensitive pathway in HIV infection has been shown. HIV infects and induces apoptosis of circulating CD4 T and CD34 multi-potent hematopoietic progenitor cells.

Keywords: ATM, Caspase, CCR5, CXCR4, gp120, Lymphocyte-specific protein tyrosine kinase, Negative factor, Nuclear factor (NF)-κB, Phospholipase C, Signaling pathways.

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1. INTRODUCTION

The HIV replication cycle depends on the interactions of viral proteins with a large number of host cell factors. The first interaction between HIV and target cells begins with the linkage of the trimeric viral surface glycoprotein gp120 to the cellular CD4 receptor [1]. This interaction activates conformational changes in gp120, and this enables the recognition of CC -chemokine receptor 5 (CCR5) or CXC-chemokine receptor 4 (CXCR4) co-receptors [2, 3]. Two key biological events will occur, *i.e.* membrane fusion and signaling transduction.

2. SIGNALING PATHWAYS THAT ARE ACTIVATED *VIA* HIV GP120 AND CHEMOKINE CO-RECEPTORS

Chemokine receptor signaling is reported as a moderator for cell migration, transcriptional activation, as well as cell growth and differentiation. Heterotrimeric G-proteins (α, β andγsubunits in a heterotrimeric) are activated through coupling to the G protein-coupled receptor CXCR4. A wide range of classes of Gα are found (Gas, Gai, Gaq, Ga12/13), however, it seems that CXCR4 is specifically linked to Gai and Gaq. The Gaq proteins activate phospholipase C-c (PLC-c), hydrolyzing phosphatidylinositol- 4, 5-biphosphate (PIP2) to inositol triphosphate (IP3) and diacylglyerol (DAG). These events result in calcium fluctuation and activation of different isoforms of Protein Kinase C (PKC) [4]. Gai-coupled Src-family kinases activates the lipid kinase PI3K, also PI3Kc is activated *via* direct coupling of Gβ,γ to the regulatory subunits of PI3Kc [5, 6]. Protein kinase B (PKB/Akt) and mitogen/extracellular signal-regulated kinase (MEK-1) and extracellular signal-regulated kinase (ERK1/2) are downstream of PI3K and function in cell survival and proliferation. Moreover, PI3K stimulates the tyrosine phosphorylation of focal adhesion complex components including proline-rich tyrosine kinase (Pyk2). Pyk2 has an important role for cell migration and cell adhesion [7]. Also, PI3K is upstream of the critical nuclear transcription activator NF-κB, regulating gene expression in the face of inflammation and activating HIV proviral gene expression [8].

Furthermore, coupling of HIV-1 gp120 to CCR5 or CXCR4 causes a faster activation of Pyk2 PI3K, Aktb, Erk-1/2 [9, 10], and CD4/CXCR4-dependent

NFAT (nuclear factor of activated T cells) nuclear translocation [11]. It was reported that gp120 mediates chemotaxis, actin cytoskeleton rearrangement [12, 13] and activation of an actin depolymerization factor cofilin for viral intracellular migration in resting CD4 T cells. Cofilin activation leads to an increase in cortical actin dynamics and actin treadmilling, and thereby promoting the movement of the viral pre-integration complex toward the nucleus [13]. As recently reported, a few HIV particles might be sufficient to activate signaling through CXCR4 [14]. CCR5 signaling has found to foster expression of genes belonging to MAPK signal transduction pathways and genes regulating the cell cycle [11]. Also, HIV infection typically leads to chronic activation of the immune system, with profound changes in quantity and quality in the T cell compartment that the basal level of phosphorylation is found to be increased in CD4 and CD8 T cells, probably due to the elevated levels of immune activation observed in advanced disease [15].

The significance of chemokine co-receptor signaling for viral infection remains controversial. In fact, the inhibition of co-receptor signaling did not inhibit HIV-1 replication [16]. Furthermore, CCR5 mutants without its signaling ability to mobilize calcium show no remarkable impairment in viral entry and replication in Hela-CD4 cells [17]. Besides, many studies have described the modulation of cellular functions by HIV gp120 signaling, from causing neurotoxicity to apoptosis. Also, stimulation of resting CD4 T cells of infected patients with gp120 resulted in induction of viral replication [18]. On the other hand, the gp120-mediated binding of HIV-1 virions to DC-SIGN can greatly stimulate the ability of virus to infect CD4 negative and coreceptor-positive cells that come in contact with the DC-SIGN expressing cell. For viral entry into the dendritic cells, DC-SIGN does not function as a receptor, it rather encourages efficient infection in *trans* of cells that express CD4 and chemokine receptors [19].

3. THE ROLE OF HIV REGULATORY AND ACCESSORY PROTEINS ON CELLULAR SIGNALING PATHWAYS

3.1. The Role of HIV Nef Protein

HIV contains several regulatory and accessory proteins (Tat, Rev, Vif, Nef, Vpr

CHAPTER 6

Determinants of HIV Pathogenesis Related to Disease Progression

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Abstract: HIV infection is regarded as one of the most important causes of mortality disease worldwide. The pathogenesis of HIV infection is complex and a multi-factorial process that is influenced by both viral and host factors. These factors play an important role in disease progression in HIV infected people. The HIV infected individuals eventually develop AIDS in a different progressive rate. The biological correlates to progression rate toward AIDS remain to be elusive. A variety of factors including host genetic susceptibility, immune function, viral genetic variability and co-infections with several microbial agents may affect the rate of progression of infection. This chapter provides information on most important factors that regulate the rate of progression of HIV infection toward AIDS.

Keywords: AIDS, CCR5, CXCR4, Cytokines, Dendritic cells, HIV, HLA-B27 antigen, HLA-B 57 antigen, Interferon gamma, Pathogenesis.

1. INTRODUCTION

In 1981, a new syndrome was observed in the United States that was determined by a profound unexplained immune deficiency [1]. Patients presented with abnormal infections and cancers such as *Pneumocystis jiroveci* (carinii)

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pneumonia and Kaposi's sarcoma. This Acquired Immune Deficiency Syndrome (AIDS) consisted of a marked reduction in CD4 T cell numbers and enhanced B-cell proliferation and hyper-gammaglobulinemia. This latter finding most likely reflects immune activation, which has recently been reappreciated as a major cause of the pathogenic pathway. In this regard, chronic inflammation has received better attention as a cause of cancer, cardiovascular diseases, and other co-morbidities appearing in long-term HIV infected people [2 - 4]. HIV-1 infection has increasingly developed around the world and become a dominant cause of death in infectious diseases in some areas. Following infection with HIV-1, the clinical course and the rate of progression toward AIDS seem to be highly variable among patients.

In fact, the rate of progression toward AIDS includes three basic types: (i) classical progression course (the most common clinical course), when AIDS becomes apparent after an interval of three to 10 years after seroconversion; (ii) long-term non-progression (LTNP) when seropositive patients remain AIDS-free for more than 10 years. In this group there are two subgroups: 1, virologic controllers who maintain the viral load below 2,000 RNA copies/mL and 2, elite controllers who have undetectable viral load or below 50 RNA copies/mL; and (iii) rapid progression (RP), where AIDS spreads within two to three years of infection [5 - 7]. Such clinical courses of progression toward AIDS depend on possible combinations of viral, host and environmental factors. In this chapter, we outline the most important factors that seem to regulate the HIV-1 infection rate of progress to AIDS.

2. DETERMINANTS OF HIV PATHOGENESIS

2.1. Host Genetic

Generally speaking, the host genetic variability contributes to determine whether an individual is susceptible or resistant to potentially pathogenic infections. Host genetic factors have a great role in the consequences of complicated or multi-factorial diseases such as AIDS which are also regarded as important to regulate disease progression rates. With regard to AIDS, several reports have shown the strong and/or weak associations between certain host genes and the variable rates

of progression toward AIDS. The selective host genes and factors which are suspected to contribute to the progression rate from HIV infection to AIDS can be divided into two categories:

A. Genes which encode cell-surface receptors or their ligands
B. Genes within human leukocyte antigens (HLA) and Killer cell Immunoglobulin-like Receptors (KIRs) regulating host immune responses to infection.

A. Genes Encoding Cell-surface Receptors or their Ligands

The entrance of HIV into cells occurs through an interaction with both CD4 and chemokine receptors of seven trans-membrane family, CCR5 and CXCR4. CCR5 exhibits different variants in its coding region, the deletion of a 32-bp segment named CCR5-Δ32 (CCR5 delta 32) results in a nonfunctional receptor, and multiple studies suggest that the existence of a single copy of this mutation causes the progression toward AIDS to dealy by about two years as it prevents HIV infection; rather, two copies of the gene establish a strong protection against HIV entry, albeit it is not a complete protection. This allele is observed in about 10% of Europeans, although rare in Africans and Asians. Beyond the genetic determinants of CCR5 expression, it is suggested that an increased number of CCL3L1 gene copy (encoding the natural ligand of CCR5, MIP-1α) may decrease the risk of HIV infection and cause a delay in clinical progression in HIV-infected subjects [5, 8 - 10].

B. Genes within Human Leukocyte Antigens (HLA) that Regulate Host Immune Responses to Infection

Host defenses have a great role in the course of HIV acquisition. The importance of diversity of T-cell recognition in disease control was suggested after realizing that homozygosity for class I HLA molecules is associated with an accelerated disease course [11]. On the other hand, certain class I HLA types are associated with a more benign disease course. It has been reported that HLA-B*27, HLA-B*57and HLA-Bw*4 exert a preventive impact with regard to progressive AIDS in patients with HIV-1 infection [12]. An immunological description for the defective role HLA B27 plays in HIV disease is that $B27^{+}$ patients show certain

CHAPTER 7

HIV Systems Biology

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Abstract: The human immunodeficiency virus (HIV) belongs to the lentivirus a subgroup of Retroviruses belongs to the Retroviridae family that attacks the immune system. The last stage of HIV infection is AIDS. HIV is absurdly simple, albeit surprisingly complex. The virus is composed of nine genes encoding 15 different proteins. The literature has reported a large number of protein interactions of HIV and human proteins. Accordingly, many human host factors have been described to be important for HIV infection and replication. Systems biology (also known as Systeomics) is an approach to study systematically complex interactions within biological systems, and to integrate and analyze complex data sets from multiple experimental sources. Long-term non progressors are patients who remain AIDS-free for more than 10 years. In this group there are two subgroups: 1. virologic controllers who maintain the viral load below 2,000 RNA copies/mL and 2. elite controllers who have undetectable viral load or below 50 RNA copies/mL. Systems biology study of elite controllers provides an opportunity to analyze the immune system response which is uniquely endowed with the capacity to retain a long-term control of HIV replication.

Keywords: AIDS, Antiretroviral therapy, Elite controllers, HIV, Host cell, Immune system, Interactions, Long-term non progressors, Replication, Retroviridae, Retroviridae, Systems biology.

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1. INTRODUCTION

Systems biology refers to an interdisciplinary approach whose focuses is to systematically describe complex interactions between all parts of biological systems, as to elucidate novel biological rules appropriate to estimate the behavior of biological systems [1]. The approaches of systems biology represent the integration of different data types and it is the most challenging field to discover interactions between genes, transcripts, proteins, metabolites, and epigenetic regulators [2]. A hypothesis-driven analysis understands relationships intuitively and then tests them; in this regard, systems biology discloses relationships between independent sets of observations to model complex networks [3, 4]. Major advances in high throughput technologies may generate large amounts of data and a wide variety of multi-dimensional assays are available for an accurate characterization of many of the elements essential to biological systems such as: A) genomics including Single Nucleotide Polymorphisms (SNPs), recombination and Chromosomal Copy Number Variation (CNV); B) epigenomics and DNA post-translational modifications such as methylation and acetylation, C) transcriptomics including mRNA expression, microRNA expression, differential transcript detection, RNA interference screening, D) Proteomics including protein expression and localization, protein-protein interaction and E) Bioinformatics. This list can be extended with newly emerging trends, such as lipidomics, metabolomics, interactomics, localizomics, phosphoproteomics, and poly-chromatic flow cytometry made possible by newly available, high-throughput, multi-dimensional technologies [5, 6].

Complex interactions take place between HIV-1 and host target cells, where all stages of the virus infection cycle rely on the strengthen of cellular proteins and basic machineries by viral proteins [7, 8]. Once host cells infected by HIV-1, active interactions between the host and pathogen occur. The efficiency of viral infection and following progression are determined by the ultimate equilibrium among the interactions. To respond viral invasion, HIV infected cells develop different antiviral tactics including antiviral mechanisms in innate, cellular and humoral immune defenses. In contrast, the virus uses strategies against such host cellular responses [9, 10]. The pathogenesis mechanism of HIV disease is multifactorial and multiphasic and it changes in different stages of the infection

[11]. Many factors, including host genetics and epigenetics, HIV strain variation, reservoirs of pro-viral DNA integrated into the human genome and co-infection with hepatitis C virus (HCV) affect the pathogenesis of AIDS [12]. Comprehensive network analysis by system biology approach establishes a promising source to assess the interactions between the host and HIV infection and the role their functions play in the pathogenesis of AIDS. Research efforts focus on a system biology approach designed for identifying multi-parametric signatures of the efficacy of protection, prevention, and treatment through classifying wide range of observations and describing mutual relations in what formerly regarded as distinct [13, 14].

2. HIV-1-HUMAN PROTEIN INTERACTION NETWORK

HIV is absurdly simple, but surprisingly complex. The virus contains a mere 9000 bases of RNA - one millionth the amount of human cell's genetic material-and a small place of nine genes coding a few 15 proteins [10]. Nevertheless, Ptak and *et al.*, identified 1448 human proteins interacting with HIV-1 composed of 2589 unique interactions between HIV-1 to human protein. Data analysis determined direct physical interactions (binding) and indirect interactions (up-regulation through signaling pathway activation) by 32% and 68%, respectively. Surprisingly, it was found that 37% of human proteins in the database interacted with more than one HIV-1 protein. The mitogen-activated protein kinase 1, for example, shows significantly different interactions with 10 various HIV-1 proteins. Furthermore, many interactions have been reported for the HIV-1 regulatory protein Tat and envelope proteins: 30% and 33% of total interactions were identified, respectively. The database is readily accessible at http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/ and it is cross-linked to other National Center for Biotechnology Information databases and softwares *via* Entrez Gene. The study aims to define main factors to improve therapeutic interventions and to develop an effective vaccine [15 - 18].

3. MICRORNAS AND HIV-1: COMPLEX INTERACTIONS

Cellular miRNAs maintain the replication of HIV in two ways: target of HIV RNA or targeting the mRNAs which encode host cell factors involved in HIV

CHAPTER 8

HIV/TB Co-Infection

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Abstract: In HIV infected patients, tuberculosis is the leading cause of death through the world. According to some World Health Organization (WHO) reports, the risk of tuberculosis disease in People Living with HIV (PLHIV) is about 10-20 times greater than people without HIV. The risk of developing tuberculosis disease in PPD positive HIV infected is about 10% annually but in HIV un-infected people is about 10% throughout their life. HIV accelerates the progression of tuberculosis infection toward disease both in recent and latent infection of TB. Pulmonary tuberculosis is the most common type of TB and its symptoms are related to the immune status of the patients and the level of progression to AIDS. Usually, signs and symptoms of tuberculosis are mild and it is difficult to diagnose. In smear negative pulmonary TB which is mostly observed in advanced HIV infection, mortality and morbidity would be higher due to the delay in establishing the diagnosis. Considering that reactivation of Latent TB (LTB) to active tuberculosis is more prevalent in PLHIV compared to HIV negative people, the diagnosis of LTB infection would be an important priority and screenings for TB should be done periodically among PLHIV as a priority. Any PLHIV with suspected LTB is eligible for isoniazid (INH) prophylaxis. All PLHIV with tuberculosis disease should be under Antiretroviral Therapy (ART) irrespective of CD4 cell count.

Keywords: AFB, AIDS, ART, CD4 cell, LTB, PLHIV, Prophylaxis, PPD, Tuberculosis, XDR-TB.

1. INTRODUCTION

In HIV infected patients, tuberculosis is the leading cause of death through the

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world. Overall, at least one third of 34 million people who are living with HIV are infected with tuberculosis. According to the WHO report, during 2012 about 8.6 million new cases of tuberculosis were diagnosed globally, and 13% of them (1.1 million) were co-infected with HIV. On the other hand, among 1.1 million deaths due to tuberculosis, 24% (350000 cases) were co-infected with HIV. Also, about 1.8 million people died from HIV infection in 2010 among whom 35000 cases were due to tuberculosis [1 - 4].

In susceptible people, *Mycobacterium tuberculosis* is transmitted through cough, sneezing, crying, shouting and singing. After entering the body, in 2-12 weeks the immune system identifies the microorganism and initiates a response. In people with normal immune status, the immune response controls the infection and thus the signs and symptoms of the disease are not manifest. But, viable bacilli may remain in several tissues of the hosts' body without producing any symptoms for several decades [5]. This situation is known as Latent TB infection (LTB), and the people with latent TB infection do not transmit the infection [6]. After several years, if the immune system is defective for some reason such as malnutrition, malignancies, chemotherapy and HIV infection, LTB can turn into tuberculosis disease [7, 8]. With regard to HIV infection, tuberculosis may be seen in any stage of HIV infection with any CD4 count, although the symptoms of the patients can be related to the CD4 cell count. It is noteworthy that poverty and crowding are the two major predisposing factors for tuberculosis [8].

2. INTERACTION OF TB AND HIV

2.1. The Effect of HIV Infection on Active Tuberculosis

HIV accelerates the progression of tuberculosis infection toward disease both in recent and latent infection of TB. In fact, HIV infection is the most important risk factor of tuberculosis reactivation. In co-infected TB/HIV patients, the risk of reactivation of tuberculosis is about 8-10% annually, but in HIV negative people, it would be about 5-10% throughout their life.

2.2. The Effect of HIV Infection on Tuberculosis Transmission

Tuberculosis is one of the most common opportunistic infections in People Living

with HIV (PLHIV), especially in areas with high prevalence of TB. By increasing the number of tuberculosis disease, the chance of TB transmission would increase throughout community and of course the rate of multi-drug resistance TB would also increase due to inappropriate treatment [9].

2.3. The Effect of HIV Infection on Tuberculosis Symptoms

Pulmonary tuberculosis is the most common type of TB and its symptoms are related to the immune status of the patients. The pulmonary TB in PLHIV with CD4>350, is similar to HIV negative patients; but in people with CD4<200 the manifestations are different. In lower CD4 cells count, patients would usually have negative sputum smears without cavitation, with middle or lower lobe infiltration in addition to lymphadenopathy. In advanced HIV infection, the rates of extra-pulmonary TB increase [10].

2.4. The Effect of Tuberculosis on HIV Infection

In HIV/TB co-infection, HIV related immunodeficiency is exacerbated and tends to manifest more opportunistic infections such as candida esophagitis, cryptococcal meningitis and *pneumocystis jiroveci* infection [11 - 13].

3. CLINICAL SIGNS AND SYMPTOMS

In LTB, the patient has inactive microorganism in some parts of body without any sign and symptom while in active tuberculosis, the signs and symptoms are related to the CD4 cell count. When CD4>350, the clinical manifestations are similar to HIV negative patients, hence upper lobe infiltration with or without cavitation is seen [14]. The symptoms of extra-pulmonary TB are mostly relate to the site of infection.

The important types of HIV/TB co-infection are pulmonary TB, smear negative pulmonary TB and extra-pulmonary TB. In pulmonary TB, typical signs include productive cough, fever, night sweat, chest pain and hemoptysis may be seen and are related to the stage of HIV infection. However, the patient may sometimes be asymptomatic, and in 22% of the co-infected patients with pulmonary TB, chest X-ray can be normal [14]. In smear negative pulmonary TB which is mostly observed in advanced HIV infection, mortality and morbidity would be higher due

CHAPTER 9

HIV and Hepatitis Viruses Co-infection: A Closer View of Their Interactions and Clinical Consequences

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Abstract: Due to sharing common routes for transmission, a significant portion of HIV infected patients are co-infected with hepatitis related viruses. It is well documented that the prognosis, pathological pathways, immunological aspects and finally drug responsiveness are different between mono versus co-infected patients. Although the detailed mechanisms regarding disease exacerbation during HIV and hepatitis virus co-infection remain uncovered, recent findings are promising in the better understanding of the interactions that, in turn maybe valuable in drug discovery.

Close interaction of viruses at common site of replication, synergic actions of proteins, changing the immune response and remodeling the cell milieu through miRNA profile are among possible manners of cooperation/counteraction between HIV and hepatitis viruses that are taken into consideration here.

As HIV infection tends to accelerate the progression of HCV and HBV infections, clinical management of this patient group must be considered more seriously. All HIV cases should be tested for HCV and HBV serological/molecular markers for further

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management in clinical setting and special therapeutic trend for virus control also should be employed as well.

Keywords: Anti-retroviral therapy, Apoptosis, Co-infection, HBV, HCV, Hepatitis, Hepatocyte, HIV, Immune modulation, Stellate cell.

1. INTRODUCTION

With more than 30 million infected patients worldwide, the Human immunodeficiency virus (HIV) remains as a major human pathogen in the 21st century. Among the clinically important pathogens that may affect HIV infection, hepatitis-related viruses are of considerable importance. In fact, many previous studies have provided evidence that the prognosis, pathological pathways, immunological aspects, and finally, drug responsiveness are different between HIV infected and HIV/hepatitis co-infected patients [1 - 3]. Despite the significant adverse clinical consequences of HIV/HBV and HIV/HCV co-infections, the details of underlying molecular mechanisms of pathogenesis during viral co-infections remain unidentified [2, 4]. In special groups such as IV drug users (IDUs), HCV co-infection is higher and several studies showed that almost 50-90% of HIV infected people with positive history of needle sharing are also co-infected with HCV [2, 3].

In this chapter, we discuss the main molecular interactions between HIV and hepatitis-related viruses, as well as its consequences on the course of pathogenesis and clinical significance.

2. THE CLINICAL SIGNIFICANCE OF CO-INFECTION WITH HIV AND HEPATITIS-RELATED VIRUSES

Due to sharing common routes for transmission, approximately 30% of patients infected with HIV are also co-infected with HCV in some western nations [5]. Also, among the HIV-infected populations, HBV co-infection ranges from 6% to 14% in low prevalence areas [1]. Nonetheless, both HCV and HBV co-infections accelerate the progression of HIV infection toward AIDS and AIDS-related diseases [1, 2]. On the other hand, the complications of chronic hepatitis such as liver fibrosis, steatosis and Hepatocelluar Carcinoma (HCC) tend to develop faster

in co-infected patients [1, 2, 4, 6].

The molecular mechanisms related to pathogenesis and clinical manifestation of HIV and HCV-related diseases seem to be completely different among mono-infected and dually infected patients, indicating the clinical importance of their interactions [4, 6]. In co-infected HIV/HCV patients, the desirable control of viral replication seems to be less achievable, both theoretically and in experimental settings. To date, epidemiological studies have supported an association between lower CD4 counts, higher HCV persistence and faster progression of liver disease, suggesting an important role for HIV co-infection in the pathogenesis of chronic liver disease [7]. On the other hand, HCV chronic infection may lead to over activation of CD4 cells which results in consequent depletion that would finally accelerate the progression of AIDS [6, 8, 9]. HIV infection tends to accelerate the progression of HCV infection. Higher HCV viral loads in serum and liver cells, exacerbation of progression toward fibrosis (at least three times more than mono-infected HCV patients) and rapid progression to cirrhosis are seen in co-infection with HIV/HCV [10 - 12].

Similar to HCV, HIV infection may exacerbate HBV infection which is always associated with an accelerated fibrosis, liver malfunction and development of HCC, albeit the mechanisms remain largely unidentified [3, 13]. The anticipated immunodeficiency following HIV infection, highly affects of natural course the HBV infection including longitudinal viral persistence, viral reactivation, less seroconversion and therapy unresponsiveness. High viral DNA load and low HBeAg clearance rate have been reported in association with lower CD4 count in untreated HIV/HBV patients [3]. Overall HIV tends to accelerate the progression of chronic HBV infection and liver failure. Also, HIV tends to increase HBV viral load in serum, while an increased risk for cirrhosis and earlier liver failure are anticipated. Additionally, the rate of reactivation of HBV in chronic carriers is increased. But several studies did not support the direct impact of HBV on HIV progression. Overall in HIV patients co-infected with HCV or HBV, the progression to end stage liver disease seems to be faster than mono infection [3].

GB Virus C (GBV-C) is a human flavivirus, recently separated from other flaviviruses and categorized in the *Pegivirus* genus. The GBV-C is a lymphotropic

CHAPTER 10

Testing for HIV Infection

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Abstract: An HIV test detects immunoglobulins against the virus or the genetic material (DNA or RNA) of HIV in the blood or specimen. P24 antigen, as a HIV core protein, momentarily becomes visible in the bloodstream during the ramp up phase when HIV-1 RNA concentration is increased up to 10,000 copies/mL.

Current rapid diagnostic tests possess high sensitivity and specificity (> 99%) and could be practical for screening individuals as they provide results in 20 minutes or less. A positive rapid HIV test results should be verified with using a supplemental test (namely, Western blot or RNA). The Western blot (an immunoblot test) detects antibodies to viral proteins and it is performed to confirm two positive ELISA tests. This confirmatory test is the gold standard among the diagnostic tests of HIV infection. ELISA is the most common HIV test performed to assay antibodies to HIV. One of the EIA-based tests is p24 antigen. New combined fourth-generation EIA antigen-antibody tests p24 antigen and anti-HIV-1/2 antibodies simultaneously. PCR is used for finding the DNA or RNA of HIV in white blood cells. This technique has high sensitivity and specificity and detects very small number of viral particles.

Keywords: DNA, Eclipse phase, ELISA, HIV, IFA, Immunoblot test, PCR, Rapid tests, RNA, Viremia, Western blot.

1. INTRODUCTION

The diagnosis of primary and incident HIV infections plays a major role in both prevention and treatment. In general, HIV test detects immunoglobulins to HIV or

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the genetic material (DNA or RNA) of HIV in the blood or other specimens. The test for HIV infection may be performed for a variety of reasons including detection of HIV infection in suspected individuals with risk factors or people with signs of HIV infection, screening of blood, blood products and organ donation as to prevent the transmission of HIV, HIV screening tests among pregnant women and for neonates who are born to a HIV-positive woman [1].

2. STAGES OF THE ACUTE PRIMARY HIV INFECTION: IMPLICATIONS FOR HIV TESTING

After transmission of HIV, an initial "eclipse phase" is produced. In this phase, infection can be identified in the local site of infection; however, dissemination is not yet available at detectable levels in the systemic circulation. The eclipse phase lasts as long as 10 days and later viral replication increases to peak levels when disseminated to lymphoid tissues and systemic circulation. In the next phase, ramp up phase of viremia or window period, HIV antibodies could not be detected. The period from infection with HIV to the point where antibodies to HIV are discovered in the bloodstream is referred as the window period or seroconversion . In this phase, an individual infected with HIV can transmit virus, even though an HIV test remains negative [1].

Fiebig *et al.*, categorized acute viremia and early seroconversion into six stages considering viral replication and evolving antibody responses [2]:

Stage I: Detection of HIV-1 RNA in the blood.

Stage II: After seven days, detection of p24 antigen, (a viral core protein, momentarily found in the bloodstream during the ramp up phase when HIV-1 RNA concentration is increased up to 10,000 copies/mL, and before the development of detectable HIV antibodies), intense inflammatory response described with high levels of cytokines and chemokines or "cytokine storm", appearance of a cellular immune response drawing escape mutants, symptoms of acute retroviral syndrome (*i.e.* fever, rash, night sweats, severe fatigue, headache, diarrhea, pharyngitis, arthralgia and myalgia) in some patients.

Stage III: Within ~five days after positive results obtained with p24 antigen test,

detection of HIV-1 antibodies (IgM) with sensitive enzyme immunoassays (EIAs) (third-generation EIAs, 1-2 weeks after the appearance of primary retroviral signs).

Stage IV: About three days after positive results obtained with sensitive EIAs, a positive or negative Western blot test.

Stage V: The development of a positive Western blot about one month following the onset of infection (Western blot positive and P31 antigen negative).

Stage VI: Western blot positive, p31 antigen positive [2].

3. THE INITIAL DIAGNOSTIC TEST FOR HIV INFECTION

3.1. Rapid Diagnostic Tests

Current rapid diagnostic tests for HIV are generally antibody-based assays. They possess high sensitivity and specificity (> 99%) and could be practical for screening individuals as the results are generated in 20 minutes or less. Six FDA-approved rapid tests determine antibodies to HIV in blood, serum, or oral fluid samples. Before establishing the final diagnosis of HIV infection, a positive rapid HIV infection test should be verified using supplemental tests (namely, Western blot or PCR). If supplementary testing is negative or indeterminate, a testing should be performed on a blood sample gathered four weeks after the initial positive rapid HIV test. Six rapid tests are approved by the FDA for the diagnosis of HIV-1 and HIV-2 so that both can be discriminated. An increasing application of point-of-care leads to decreasing the number of early cases of HIV infection that are discovered by rapid HIV antibody tests for HIV screening. However, rapid HIV tests are considerably available in environments with limited resources and take benefits from same-day results [3 - 5].

3.2. Enzyme-linked Immunosorbent Assay (ELISA)

ELISA is the most common HIV test performed to assay antibodies to HIV. If antibodies to HIV are detected (positive), in order to confirm the diagnosis, the test is usually repeated. For negative ELISA, there is no need for supplementary tests. The drawbacks of such highly sensitive test are false positives, variation in

CHAPTER 11

When to Start Antiretroviral Therapy

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Abstract: Antiretroviral therapy (ART) has led to dramatical improvements in the prognosis of people living with HIV. ART suppresses viral replication, reconstitutes the immune system, decreases the possibility of many HIV-related complications, and lowers the risk of HIV acquisition. Despite of substantial health benefits of ART, it accompanies its own limits. ART does not cure HIV infection and needs taking several medicines simultaneously. It causes numerous adverse effects, it is expensive and efficacy requires complete adherence. Poor adherence leads to emergence of resistance virus and finally treatment failure.

However ART is now recommended for everyone with HIV regardless of CD4 count and stage of infection. Evidences in favor of earlier ART initiation include clinical trials, better understanding of viral dynamics, effect of inflammation on body organs, newer medications that are better tolerated, data derived from cohort studies, and public health benefits of ART in preventing HIV transmission. Concerns about early ART initiation include effect of long term ART toxicity, impact of possible ART non-adherence on viral resistance, and feasibility of implementing early ART.

Based on currently existing evidences, ART is recommended for all HIV-infected individuals. The suggestion is the strongest for people with lower counts of CD4 cells, or for those with pregnancy, history of AIDS-defining illness, any type of tuberculosis, acute opportunistic infections, HIV associated nephropathy, HBV co-infection and for all children <2 years old.

Keywords: Antiretroviral drugs, Antiretroviral therapy, ART benefits, ART feasibility, ART initiation, ART limitation, Early ART, Health benefits, Time of ART initiation, Viral suppression.

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SeyedAhmad SeyedAlinaghi (Ed.)

1. INTRODUCTION

Natural course of HIV infection is described by ongoing viral replication, continued depletion of CD4+ T lymphocytes that leads to unrelenting immune system destruction, development of opportunistic diseases and premature death. As well according to recent studies, HIV is accompanied with an increase in the risk of serious non-AIDS conditions like cardiovascular, renal and liver diseases as well as neurocognitive deficits and non-AIDS-defining cancers. Many of these effects can be mediated through continued activation of immune system and unremitting inflammation in various organ systems [1].

The introduction of powerful Antiretroviral Therapy (ART) has considerably improved the prognosis of people living with HIV. Today, HIV is not a fatal disease, and can be controlled through retaining adequate adherence to antiretroviral (ARV) drugs over the long term [2]. Potent combination ART, classically consisting of three or more ARVs, show pronounced improvement in the health and survival rates of HIV-infected subjects in those with access to ARVs. At present, more than 20 ARVs in six classes are accessible. It is possible to combine these in order to launch several effective regimens for initial and subsequent treatments. ART suppresses viral replication, reconstitutes the immune system, decreases the risk of numerous HIV-related and "non-AIDS" complications, and also reduces the risk of HIV acquisition [3].

Despite significant health benefits, ART has its own limits. It does not cure HIV infection and it needs taking several medicines for lifetime. ART is associated with diverse adverse effects (some severe), it is expensive, requires high adherence to be effective and to avoid the appearance of resistance, and occasionally fails (because of the patient's poor adherence or other factors). The absence of success in an ART regimen accompanied by drug resistance indicates that the succeeding regimens are less likely to suppress the virus [3].

Increasingly, gathering evidences state to the benefits of ART even for individuals with high counts of CD4. It seems that ART reduces immune system stimulation and protect against many of such morbidities through virologic suppression; nevertheless, it may cause dysfunction of immune system and may not fully

reverse disease processes. The favorable effects of ART may be lessened for patients who start ART with lower counts of CD4 cell. Additionally, the risk of some ARV-related adverse events is greater for those starting ART at lower levels of CD4 [4].

The argument about 'When to Start' ART has raged since the introduction of zidovudine in 1987 [4] until recently when a clinical trial revealed offering ART to all HIV-infected people, regardless of CD4-cell count to improve outcome of PLWH [5].

2. EVIDENCES IN FAVOR OF EARLIER ART INITIATION

2.1. Evidences from Clinical Trials

A major international randomized clinical trial has showed that PLWH have a considerably decreased risk of developing AIDS or other serious illnesses if they start ART earlier, at the time of higher CD4+ T-cell, instead of waiting until the CD4+ cell count falls to lower levels. The study population was 4685 PLWH (treatment-naive adults) at 215 sites in 35 countries with an average follow-up of 3 years. In early 2015, the NIH released the study results early after an interim analysis revealed that, although the overall event rate was low (<3% over 3 years), the risk for serious illness or death was reduced by 53% in the early-treatment group. The reduction was greater for AIDS-related events than for non-AIDS events (70% and 33%, respectively).

2.2. Effect of Viral Dynamics

Viral dynamics studies demonstrated how fast rounds of *de novo* virus infection occur, producing 1 to 10 billion new viral copies per day [6]. With such large scale viral replication, both the viral life cycle and the half-life of infected CD4 T cells were estimated as short as one day or less with several million CD4 T cells being infected each day [7]. These findings indicate the great destructive effects of the viral replication cycles on the immune system even over the stage of "clinical latency" [6]. Therefore, it is necessary to onset impediment of the unremitting rounds of viral replication as soon as possible [4].

CHAPTER 12

Antiretroviral Therapy (ART) in Pregnant Women

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Abstract: Interventions to prevent mother-to-child transmission (MTCT) of HIV have become increasingly efficacious over time. Furthermore, regimens and treatment protocols have become increasingly simplified to facilitate coverage at all levels of care and reduce time-to-initiation of prophylaxis regimens. Yet, a substantial number of HIV-infected pregnant women are still not being reached by PMTCT services globally. Although a challenging prospect, we have the tools to end the transmission of HIV from mothers to babies – now is the time for communities to redouble efforts to more effectively implement PMTCT strategies to reach this critical goal.

Keywords: Antiretroviral, Breastfeeding, Guidelines, HIV, Infant, Option B+, Perinatal, Maternal, Prevention of Mother-to-Child Transmission (PMTCT), Prophylaxis.

1. INTRODUCTION

With currently available antiretroviral regimens for the Prevention of Mother-to-Child Transmission (PMTCT) of HIV, perinatal transmission may be reduced from 20-45% without intervention to less than 2% [1, 2]. Based on considerable progress in the expansion of antiretroviral therapy (ART) and PMTCT services globally, as well as implementation of more efficacious PMTCT regimens as outlined in the 2010 and 2013 World Health Organization (WHO) guidelines [3, 4], the prospect of eliminating pediatric HIV is as close as ever [5].

The "Countdown to Zero" initiative announced by the Joint United Nations

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Programme on HIV/AIDS (UNAIDS) ambitiously aims to eliminate pediatric HIV infection by 2015 [6]. However, despite improved access to antiretrovirals (ARVs), PMTCT service utilization remains suboptimal. In 2012, just 62% of HIV-infected pregnant women received ARVs to reduce MTCT [7, 8], and, in 2011, only 35% of infants born to HIV-infected mothers underwent HIV testing in the first two months of life [8]. Although the number of children born with HIV infection has declined by 58% since 2002, an estimated 240,000 infants were born with HIV in 2013 [9, 10], falling far short of what can be achieved with available biomedical interventions.

Thus a comprehensive approach that includes treatment as prevention for women, access to family planning services, universal HIV testing in pregnancy, rapid linkage to care, increased retention of pregnant women, universal access to ART during pregnancy and breastfeeding, appropriate infant prophylaxis, among other comprehensive care interventions, is critically needed.

2. HISTORICAL OVERVIEW OF PMTCT

In 1982, approximately 18 months after the recognition of the first acquired immune deficiency syndrome (AIDS) cases among adults, the epidemic was recognized among among infants in the U.S. as well [11]. Soon after, awareness of the global extent of pediatric infection began to accumulate. One of the earliest reports estimated 11% prevalence among a small cohort of hospitalized children in Zaire [12].

While zidovudine (AZT, ZDV) was approved for use among adults in 1987, it took seven additional years to fully appreciate the potential for ARVs to reduce MTCT. The landmark study, PACTG 076, was first reported in 1994 after being stopped early by the study's Data Safety and Monitoring Board (DSMB) due to overwhelming success. The study found that transmission in the placebo group was 25.5% compared with 8.3% in the AZT group, a reduction in transmission of 67% [13]. This rapidly led to changes in guidelines for treatment of pregnant women with HIV. However, widespread implementation of intravenous AZT during labor and delivery was not felt to be feasible in many resource-constrained settings and thus multiple studies were subsequently performed to evaluate

simplified oral regimens. In 1999, a study assessing short-course AZT in Thailand showed that transmission could be reduced by 50%, from 19% in the placebo group to 9% in the AZT group [14]. However, in a study from West Africa, follow-up of patients revealed a loss of efficacy over time due to high rates of HIV transmission during breastfeeding [15].

In 1999, the HIVNET 012 study found that a simple regimen of single-dose nevirapine (sdNVP) given during labor reduced the risk of transmission by nearly 50% [16]. However, enthusiasm for sdNVP quickly waned as high rates of NVP resistance were noted among mothers exposed to sdNVP. A meta-analysis of 10 studies showed that over a third of women developed NVP resistance [17]. However, the risk of NVP resistance was reduced by almost 90% if a 7-day "tail" of AZT/3TC was added after sdNVP [17].

Starting in 2010, a number of studies showed that maternal triple ARV prophylaxis was highly efficacious in reducing the risk of breastfeeding transmission. In the BAN (Breastfeeding, Antiretrovirals, and Nutrition) study, women were randomized to receive post-partum triple ARV prophylaxis, which reduced the rate of breastfeeding transmission to 3% by six months [2]. Two randomized trials, the Kesho Bora and Kisumu studies, which examined the efficacy of triple ARV prophylaxis starting late in pregnancy and continuing until rapid cessation of breastfeeding at six months, found similar rates of transmission of about 5% at 12 months of life [18, 19]. Finally, in the Mma Bana study carried out in Botswana, women were started on triple ARV prophylaxis starting between 26-34 weeks gestation and continued until weaning of breastfeeding at six months of life. Virologic suppression throughout breastfeeding was achieved by 93% of women and overall transmission was 1% through six months [1]. From a research perspective, studies have achieved near elimination of pediatric transmission utilizing simplified maternal and infant prophylaxis regimens. Yet achieving the goal globally will remain elusive unless all women are reached with these highly efficacious regimens.

CHAPTER 13

HIV Drug Resistance

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Abstract: The ability of HIV to mutate and replicate in the presence of antiretroviral therapy (ART) drugs are called HIV drug resistance. There are many reasons for HIV drug resistance happening. Some determinants are related to virus such as infidel reverse transcriptase, error-prone replication, *etc*. The appearance of drug resistance mutations and viral evolution could be a result of continuing HIV-1 replication in ART among some infected subjects. A wide range of mechanisms has been described with difference characteristics for different classes of drugs and also for drugs of a given class. New antiretroviral (ARV) drugs which are often applied in treatment-experienced patients include the entry inhibitor (Enfuvirtide), protease inhibitors (PIs) (Darunavir and Tipranavir), a C-C chemokine receptor (CCR) type 5 antagonist (Maraviroc), an integrase inhibitor (Raltegravir) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Etravirine). The overwhelming data presented in journals and at scientific meetings helps staying informed about current issues, but makes new developments a daunting task.

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Keywords: Antiretroviral therapy, Determinants, Drug Resistance, Epidemiology, Guideline, HIV, Mechanism, Novel, Prevalence, Transmission, Treatment.

1. INTRODUCTION

HIV drug resistance is defined as the ability of HIV to mutate and replicate in the presence of antiretroviral (ARV) drugs. Drug resistance has become a universally challenging issue since the introduction of first ARV drugs for the treatment of Human Immunodeficiency Virus (HIV) infection [1]. ARV drug resistance is often observed in subjects with incomplete viral suppression and can limit both the scale and duration of the treatment response. As alternative great concern, the Transmitted Drug Resistance (TDR) to newly infected persons has been reported in almost all countries with access to Highly Active Antiretroviral Therapy (HAART) [1 - 11]. Although TDR has been recognized for more than a decade, the changes and the effects with respect to treatment's responses have not been defined yet [2].

The ARV resistance patterns among recently infected populations appear to reflect geographic trends with regard to the use of ARV medications worldwide. According to the worldwide surveillance program (WATCH), the resistance rate for any ARV drugs among treatment naive individuals was 5.5% in Africa, 7.4% in East Asia, 5.7 % in Southeast Asia, and 6.4 % in Latin America compared to higher levels in North America (11.4 %) and Europe (10.6 %) [3].

It has been previously implicated that the main reason for the emergence and spread of drug-resistant HIV strains might be inadequate adherence to therapy [4]. In fact, HIV replicates and mutates at high rates *in vivo* which leads to continuous production of genetically varying horde of viral strains [1].Although most of HIV-1 variation appears from the accumulation of point mutations, recombination can be also involved in the viral variations, since leaping in genetic evolution by merging two or more distinct beneficial mutations into a single genome.

It is necessary to maintain resistance surveillance programs throughout the developing countries and to report and analyze data in a consistent and timely manner. ARV resistance was especially common in persons who received mono- or dual- drug therapy before the application of HAART regimens that composed

of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs) [7].

2. GLOBAL EPIDEMIOLOGY OF TRANSMITTED DRUG RESISTANCE

Drug resistance to ARV agents has been documented since 1989. In fact, drug resistance is one of the most common reasons for HAART failure and is generally attributable to the patient's poor adherence or low potency of the therapeutic regimen [8].

Recent data suggest that HIV-1 resistance is decreasing in patients with antiretroviral regimens which are mainly the result of applying more potent drug combinations as therapy options. In the following section, we briefly describe the global epidemiology of TDR [10, 11].

2.1. TDR in The USA

The largest study that surveyed TDR in the USA enrolled 1082 recently infected patients from 10 cities and reported the prevalence of TDR to be about 8.3%. TDR was more common in Men who have Sex with Men (MSM), compared to heterosexual men and women (12%, 4.7% and 6.1% respectively) [12]. Furthermore, the prevalence of resistance mutants was reported to be 5.4% among African–American populations, and 13% in Caucasians. In another study in the USA, the prevalence of TDR was 25% in 2005 [13, 14]. Studies of newly infected patients showed intermediate rates of TDR in Canada (8% from 1997 until 2005). Finally, the reports gain different rates of TDR in the USA between 8.3% and 27.3%, based on the epidemiological situation [15].

2.2. TDR in Latin America

With regard to the lower availability of ART, a lower distribution of TDR in these countries are expected, however, some studies from Latin America (especially Brazil & Argentina) have reported a higher frequency of TDR in these countries. For example in Argentina, a sensible growth of TDR has been documented [16]: TDR prevalence was about 1% in 2001 and 12.9% in 2005 until 2007. However, the prevalence of TDR in other Latin American countries is relatively low. In Chile, Studies showed a 2.5% increase in TDR levels from 2000 to 2005 [17].

CHAPTER 14

Serodiscordant Couples and Fertility Management

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Abstract: HIV spread in many developing countries is high as a result of homosexual, heterosexual intercourses and drug abusing. Most HIV infected individuals are attributable to heterosexual intercourse. There are several biologic and behavioral risk factors lead switching a discordant couple to concordant one such as having a high HIV viral load, living together, being uncircumcised for men, and reporting a Sexually Transmitted Disease (STD) within the six months before the beginning of consensual sex intercourse for women. Strategies on prevention includes the use of condom, abstinence and bed separation, contractual agreements for outside sexual partners, and cessation of relationships for any couple, providing early sexually transmitted disease diagnosis and treatment, antiretroviral therapy (ART), and specially designed counseling to HIV discordant couples in stable relationship. ART can protect against the HIV transmission from an infected sexual partner to an uninfected one by reducing viral replication.

Keywords: Antiretroviral therapy, Behavior and attitude, Counseling, Epidemiology, HIV serodiscordant, Pregnancy, Preventing routes, Processed semen.

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SeyedAhmad SeyedAlinaghi (Ed.)

1. INTRODUCTION

Many discordant couples have shown strong desires for having a biological child. Studies showed having their own child has positive psychological effects on quality of life (QOL) of discordant couples [1].

The risk of HIV transmission during a single episode of unprotected sexual intercourse should be explained to serodiscordant couples before any decision [2, 3]. Table **1** shows the most substantial factors that have effects on HIV transmission risk.

Table 1. The most important variables that affect transmission risk.

Stage of the disease (viral load*, CD4 count, AIDS defining symptoms)
Use of antiretroviral therapy
Source of infection
Stability and length of relationship
Anal intercourse
Genital tract lesion or infection
Circumcision of male partner
Time of menstrual cycle (maximum risk during menstruation)
Frequency of intercourse

*HIV levels in plasma and semen are not well correlated [4, 5].

Reproductive Counselors have an important responsibility regarding serodiscordant couples. Reviews and studies in African and non-African settings have investigated the efficacy of VCT (Voluntary HIV Counseling and Testing) in lowering risk behaviors and occasionally rate of HIV sero-conversion in VCT recipients. Most HIV infections in Sub-Saharan countries occur during hetero-sexual intercourses between serodiscordant couples [6]. In a previous report, 95 serodiscordant couples were studied in which a male partner was sero-positive and maintained sexual unprotected intercourse during the period of follow up. Seven months later, four women sero-converted (two of them sero-converted postpartum) [2]. Hence, we should emphasize the importance of the "Reproductive Counseling" and "Assisted Reproduction method by using sperm washing" for serodiscordant couples [2]. Since 1989, assisted reproductions using

sperm washing method were done in many discordant couples. Finally, all pregnancies without any case of female sero-conversion or pediatric infection were achieved [2, 7].

2. INSEMINATION OF HIV NEGATIVE WOMEN WITH PROCESSED SEMEN OF HIV POSITIVE PARTNERS

Processing semen from HIV positive men can reduce HIV-1 levels to undetectable levels [5, 8]. The processing method that was first described by Semprini *et al.*, consists of gradient centrifugation and repeated washing followed by swim up procedure to isolate motile and virus-free spermatozoa [8] (see Table **2**). Sperms do not describe remarkable rates of HIV receptors (CD4, CCR5, and CXCR4); as a result they are less likely to be key targets for HIV infection [4, 5]. To date, several studies have tried assisted conception explained above and all babies born to mothers using this method remain sero-negative [2 - 4, 8]. There are several techniques to assess the HIV levels after processing such as "immune fluorescence" or "detecting HIV-1 RNA copies per mL using nucleic acid based sequence amplification (NASBA)". Immune fluorescence method is not as sensitive as NASBA and hence, is not recommended nowadays [9]. We should consider that these procedures do not always remove detectable HIV-RNA. Consequently, it is strongly recommended that all samples for insemination are to be tested before insemination using NASBA or a similar sensitive assay and that only samples in which HIV cannot be detected be used [3, 9].

Table 2. Summary of studies on the safety and effectiveness of the "Sperm-washing" method.

Semprini *et al.*, [8]	• Women were inseminated with the processed semen (using sperm washing method) of their HIV positive partners during a timed insemination course and none of them sero-converted. Ten babies born to these mothers remained sero-negative.
Chrystie *et al.*, [9]	• Treatment of semen from HIV-infected men using standard procedures can reduce HIV-1 RNA concentration in the final sample to undetectable levels and this reduction is more efficiently performed using Percoll rather than Ficol gradients. • An experience of over 1000 insemination without any subsequent sero-conversion

CHAPTER 15

Aging in People Living with HIV

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Abstract: The invention and administration of novel antiretroviral therapies (ART) has led to the increased lifespan of People Living with HIV (PLHIV) especially in the developed world and thus, we are facing with increased number of HIV infected people over the age of 50 years. It seems that HIV infection may accelerate the aging process by accelerating the shortening of telomeres. Several adverse habits such as smoking and drug abuse as well as co-infection with other pathogens are more common among PLHIV. So, by increasing the age, inappropriate lifestyle and adverse habits such as cigarette smoking, drinking a lot of coffee, being physically inactive or inappropriate activity, opium and drug abuse and alcoholism put people in higher risk of osteoporosis. Several issues should be considered about aging like osteoporosis, neurocognitive impairment, cardiovascular disorders, and impairment of liver function along with the especial consideration about ART in elderly. There are several recommendations for slowing down the aging process in PLHIV. The cessation of cigarette smoking is the main step to prevent undesirable complications such as lung diseases and cancer, increased risk of heart attacks and strokes, bone mineral loss, muscle wasting and memory disorders. Drug abuse, especially some newer drugs like amphetamines and "crystal" may lead to several memory and behavioral impairment, depression and suicide. Regular exercise is another health habit that should be promoted among older PLHIV.

Keywords: Aging, ART, Cardiovascular disorders, CD4 cells, Drug abuse, Lipodystrophy, Neurocognitive impairment, Osteoporosis, PLHIV, Smoking.

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SeyedAhmad SeyedAlinaghi (Ed.)

1. INTRODUCTION

Considering the improvements in the total health globally, the numbers of old people have increased throughout the world; therefore, specific health conditions that are related to older age would be of more importance in this age group, including HIV infection. In fact, the invention and administration of novel antiretroviral therapies (ART) has led to the increased lifespan of People Living with HIV especially in the developed world and thus, we are facing with increased number of HIV infected people over the age of 50. According to recent studies *it is estimated that by 2015, over half of all PLHIV in US will be over 50 years of age or older* [1].

On the other hand, wider educational programs throughout the world have resulted in wider HIV testing among all age groups which should be regarded as another reason for increasing numbers of known HIV infected people especially in age 50 and older [2]. Evidently, certain health conditions may require further clinical care among elderly PLHIV *i.e.*, neurological and cardiovascular disorders, osteoporosis and hypogonadism. Also, in the elderly there are some particularities regarding the diagnosis, pre exposure prophylaxis, rate of progression toward AIDS, varying pharmacokinetics of ART agents, treatment adherence and drug interactions in older age groups.

According to a report on aging *"there is gender difference related to sexual activity and it was found that 71% of men and 51% of women aged 60 and older continue to engage in sexual activity"* [3]. But due to several reasons, aged people would not be likely to use condoms (*i.e.* not being afraid of pregnancy). Also, atrophic vaginitis in women and impotency and arousal difficulties in men tend to further reduce the use of condom [3]. Such reasons put older people at higher risk for Sexually Transmitted Infections (STIs) including HIV. Therefore, it is very important to discuss the proper use of barrier methods with the elderly [4]. On the other hand, the prevalence of persons aged over 50 who have a positive history of IV drug use has also increased significantly in the last several years [5]. Thereby, needle sharing that is one of the main routes of HIV transmission among youth should be considered in elderly too.

2. THE PROCESS OF AGING

There are several genetic, environmental and biological factors that are pivotal in senescence. It is important to keep in mind that senescence also occurs at the cellular level. The replication capacity of cells is related to the small fragments at the end of the chromosomes, called telomeres. The length of telomeres is associated to cell age. During life, cells reproduce hundreds or thousands of times from original cells and in each division, telomeres become shorter and shorter. When telomere is long enough, cells are young with normal function. Following the shortening of telomeres, cellular activities deteriorate and cellular division would not be possible afterward. At the end of this process, the weakening of several body systems like musculoskeletal system occurs.

It seems that HIV infection may accelerate the aging process by accelerating the shortening of telomeres [6]. Several adverse habits such as smoking and drug abuse as well as co-infection with other pathogens are more common among PLHIV. In addition, certain organic disorders tend to be more prevalent among PLHIV such as:

- Cardiovascular diseases
- Renal diseases
- Muscles weakness and weakened bones
- Lipodystrophies
- Liver diseases

Some of the above conditions may result from ART. Organic disorders may also be due to direct effect of HIV, such as HIV nephropathy, HIV cardiomyopathy and HIV enteropathy, or be the consequence of other factors such as cervical cancer due to HPV infection, heart attack and lung cancer due to smoking, and liver failure due to HCV and HBV co-infections.

3. AGING OF THE IMMUNE SYSTEM

Aging has been associated with decreased production of some cytokines like IL-2 that is important in cellular immunity and impaired production of this cytokine promotes dysfunction of T cells. When older patients are chronically infected with

CHAPTER 16

Interaction of Behavior and Biomedical Prevention

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Abstract: Today we know that for new HIV infection prevention, there are some effective and feasible programs such as needle exchange, behavioral interventions and antiretroviral therapy (ART). The main component to maintaining behavioral changes is to find novel techniques and know how to stay motivated and also use combination of techniques and methods. This is what researcher and health providers call Biomedical and Behavioral interventions in prevention of HIV infection. Current evidence confirms the efficacy of behavioral interventions in lowering HIV acquisition versus standard care or no intervention. Biomedical intervention is another effective program for HIV prevention, where medical and clinical approaches are used to decrease HIV infection. As HIV infection rates are strongly influenced by human behavior, behavioral changes has long been understood as essential to curb the prevalence of infection. In all cases where a decrease in prevalence has been observed, broad-based changes in behavior were the key of success. Besides behavior change strategies, it is necessary to consider the accessibility to novel biomedical HIV prevention modalities such as vaccines and microbicides. The combination of behavioral changes and application of medical treatment (as ARV or Drug treatment such as Methadone and preventive treatments like microbicides) is regarded as the best effective intervention aganist HIV acquisition.

Keywords: ART, Bio Behaviors, Effective, HIV treatment, Interventions, Medical treatment, Methadone, Microbicides, Vaccines.

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SeyedAhmad SeyedAlinaghi (Ed.)

1. INTRODUCTION

Human immunodeficiency virus (HIV) leads to acquired immune deficiency syndrome (AIDS) which is transmitted through contact with infected blood and bodily fluids.

Generally, HIV is associated with injection drug use and unprotected sexual contact. In other hand, although HIV infection is considered a sexual transmitted disease, there is also a strong influence of human behavior [1].

HIV leads to remarkable inflammation in the body. Some possible consequences of this inflammation are spinal cord and brain damages; dysfunction of nerve cells [1]. Neurological complications are the product of damage by the virus itself and do not usually set in, until advanced stages of HIV infection, characteristically in "AIDS" stage of infection. On the other hand, people with HIV or AIDS often develop anxiety disorders and depression. Hallucinations and remarkable changes in behavior can be experienced [1].

According to the route of transmission, several groups are at high risk for HIV acquisition, such as injection drug users (IDUs) by sharing needles and injecting equipments, non IDUs by impairment of judgment and also enhancement of sexual arousal which can lead to risky sexual behavior, commercial sex workers (CSW) by unprotected multi partner intercourse and their partners.

Drug use facilitates HIV infection progression by further compromising the immune system [2].

A reduction in the use of syringes and sexual risk behaviors of illicit drug users might have a great impact in the public health all around the world [3].

As supported by UNAIDS 2014 report on the global AIDS epidemic, the reduction in new HIV infections over the past 10 years is obviously accompanied with changes in behavior and social norms beside with increased awareness of HIV.

Today we know that for new HIV infection prevention, there are some effective and feasible programs such as needle exchange, behavioral interventions and anti-

retro viral therapy (ART).

2. BRAIN AND BEHAVIOR

The frontal lobe is an area in the brain, located at the front of each cerebral hemisphere. The frontal lobe covers most of the dopamine-sensitive neurons in the cerebral cortex. The dopamine system is associated with reward, attention, short-term memory tasks, planning, and motivation. The Frontal lobe is important for planning of movements, recent memory and some aspects of emotion as well as it is a component of the cerebral system, which supports goal directed behaviors and observed activity as a response to internal or external stimuli [4, 5].

When people wants to make changes such as lose weight, stop smoking, or accomplish another goal, there is no single solution that works for everyone. They have to try several different techniques, often through a process of trial-and-error, in order to achieve their goal. During the period of changing many people become discouraged and relinquish [5]. Therefore, changing behavior is difficult and the major practice to maintain behavioral changes is to seek new strategies and pave the ground to maintain motivations [5]. This is what researchers and health providers call biomedical and behavioral interventions in prevention of HIV infection.

3. BIOMEDICAL AND BEHAVIORAL INTERVENTIONS

In 2009, the Joint United Nations Program on HIV/AIDS (UNAIDS) reported that, the high rates of HIV infection among sex workers, as compared to most other population groups, has affected rates of heterosexual transmission of HIV particularly in low- and middle-income countries.

These trends have prompted the UNAIDS to call for an urgent redoubling of the effort in the fight against HIV/AIDS and many studies had been settled down for decrease the number of new HIV infection [6].

3.1. Behavioral Intervention

The underlying promise for the behavioral interventions is that human behaviors are mostly learned by interactions between an individual and the environment.

CHAPTER 17

Community Involvement in HIV Prevention

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Abstract: The Human Immunodeficiency Virus and AIDS (HIV/AIDS) pandemic remains a public health challenge and a significant obstacle to socioeconomic development especially in developing countries. HIV/AIDS is a serious disease and has claimed millions of lives across the world in recent years. Many Individuals, families and communities including adults and children from across the world, particularly in low-and middle-income countries have been affected by this scourge. To address this problem, community involvement in HIV/AIDS prevention has been recognized, particularly because HIV/AIDS acquisition and transmission occur through community interactions and via complex social networks. Recognition of factors contributing to susceptibility and the spread of HIV/AIDS within countries, societies, communities and populations groups is necessary in order to halt this pandemic. Recognising these factors will inform the development of strategies to address the epidemic within general communities and within specific key population groups. Networks of individuals such as sexual partners, community members and societies need to be recognised as important in HIV transmission and prevention and understanding of communities dynamics including within families, friends and acquaintances should be the first entry point for HIV/AIDS management strategies. Involvement of communities will include developing and implementing community-based approaches to HIV counseling, testing, treatment and prevention. Effective linkages of these approaches with health facility-based services and eradicating the barriers that key populations face in accessing these services are necessary measures. Improving policies and interventions including providing effective education to various key populations and subgroups will facilitate effective life-saving choices.

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Keywords: A global challenge, AIDS, Communities, Community involvement, HIV, Key populations, Public health threat, Social networks.

1. INTRODUCTION

Since its initial reporting over three decades ago, the HIV/AIDS contagion has remained a deadly disease without cure, and a significant cause of impairment in public health and development among families, communities and nations across the world. Globally, HIV/AIDS has affected individuals, families and communities with millions of lives lost. Importantly, developing nations and middle income countries are the most affected [1, 2]. Further reports on HIV/AIDS have revealed that more than 30 million people have become victims of this scourge globally, including children [3 - 6]. However, the reported HIV/AIDS prevalence across the globe is variable, with good and not so good stories. For example, it has been reported that HIV/AIDS rates in some countries such as Malawi and Kenya have been declining [3, 6 - 8], while in other countries such as Thailand and in other South East Asian countries, the HIV/AIDS rates are increasing despite earlier reports of declining trends [9]. Additionally, in some countries including the Middle East, the Pacific region, China and India, HIV/AIDS prevalence are reported to be increasing [1, 3, 10]. It has also been noted that, the determinants of susceptibility and acquisition of HIV infection include behaviors of people who have one or more commonalities and interests [10]. In recent years, the importance of community involvement in disease prevention including HIV/AIDS prevention has been recognised [11]. As such, because HIV acquisition and transmission occur between people who interact in one way or another [12], it is necessary to address HIV/AIDS issues through sociocultural networks and community groups. Recognition of the multiplicity of factors contributing to people's susceptibility and the spread of HIV infection within countries, societies, communities and groups of population is critically important to prevent and halt the transmission of this pandemic. It is therefore necessary to recognise dynamics in the society of individuals, community members and social networks in order to develop necessary strategies for prevention of HIV and protection of communities [13]. Communities including families, friends and acquaintances are the first entry point to preventing HIV transmission. Prevention can be done by providing education and reinforcing HIV

risk evading behaviors among members of such networks. The family for example, plays a key role in taking care and educating its members who are infected by HIV/AIDS [14]. Because of the advancement of HIV treatment, HIV and related opportunistic infections have become more of chronic health conditions rather than a death sentence and when many individuals are affected within a community, it is necessary to involve the whole community in addressing many complex issues of HIV prevention, including treatment options [15].

2. COMMUNITIES

Medical and public health specialists and practitioners, sociologists, anthropologies, demographers, social workers and other relevant professionals in sectors dealing with HIV pandemic hold varying perspective of what the community is [16]. However, one definition and that will be used in this chapter stands up highly and defines the community as a group of people sharing a common value system, having common needs and sharing interests and have similar or shared experiences [17]. It has also been described that, next to the families, the community is the most important framework in which an individual learns to grow and develop socially and is the center of activities which contribute significantly to the development of human values [18], including those related to HIV transmission. The community provides a space whereby its members develop a sense of attachment with each other through interaction in a variety of social groupings [18 - 20]. Many characteristics of the community structure and interaction have been identified as complex, but overall, members of the community socialise and communicate with each other to share thoughts, feelings, experiences, skills and knowledge [15, 17, 21]. These interactions offer a sense of togetherness among people and are developed in different ways in different communities [12, 21]. Societal member interactions range from simple actions including individual lovers or communities groups' interactions [13]. Communities interact when community members and groups are connected for a common goal including the sharing of resources [16, 17, 22].

Multiple and complex community factors including socio-cultural, economic and structural are involved in the interplay of HIV/AIDS matrix of infection acquisition and transmission [13, 23]. As such, in order to combat the HIV/AIDS

CHAPTER 18

Positive Prevention

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Abstract: In order to control HIV epidemic, people should avoid high-risk behaviors related to the transmission of HIV regardless of their HIV status. The practice of best known strategies for avoiding HIV infection is both true for People Living with HIV (PLHIVs) and the sero-negative people. However, HIV may be transmitted via two scenarios: the first is that the HIV-positive person is unaware of his/her sero-status, and the second is that the HIV-positive person ignores his/her sero-positivity.

Positive Health, Dignity and Prevention (PHDP) covers a broad spectrum of policies and activities not only for PLHIVs but also for all of the members of a community, hence we all have responsibilities in the control of HIV epidemic.

Positive Health, Dignity and Prevention is not just a new name for the concept of HIV prevention for and by people living with HIV, formerly known as 'positive prevention'. Implementation of PHDP would not be similar in different settings (*i.e.* available resources, stages of the epidemic, *etc.*); but in all communities, eight major components have been introduced as the framework of PHDP activities, that are: advocacy, building evidence, coverage scale up, increase in access to services, serodiscordant couples protection, influence the responsibilities of PLHIVs, stigma and discrimination reduction and scaling up and supporting the social capital

Keywords: Advocacy, Evidence based, Dignity, Health, HIV transmission, Human Rights, Most at risk populations, Positive Prevention, Prevention, Quality of life, Research, Sero discordant couples.

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1. INTRODUCTION

In order to control HIV epidemic, people should avoid high-risk behaviors related to the transmission of HIV regardless of their HIV status. The practice of best known strategies for avoiding HIV infection is both true for People Living with HIV (PLHIVs) and the sero-negative people. However, HIV may be transmitted *via* two scenarios: the first is that the HIV-positive person is unaware of his/her sero-status, and the second is that the HIV-positive person ignores his/her sero-positivity. Subsequently, unsafe sexual contacts and/or needle sharing practices are the main routes of transmission which occur after the first two states.

Tailoring appropriate and effective interventions for PLHIVs is one of the most important strategies for the control of epidemic. It means that for having a nationally effective response to epidemic, we need to get PLHIVs participation in different levels of interventions from policy making to field work [1]. HIV transmission in almost all of the cases is highly related to human behaviors. Unfortunately, changing high-risk behaviors to safe behaviors is not usually simple, and the desirable change in marginalized and most at risk populations is considerably harder compared to the other sections of a community. Moreover, anti-retroviral therapy increases the lifespan of PLHIVs and decreases their morbidity. Accordingly, a larger population of PLHIV should control their risky behaviors for halting the spread of the infection. For example, practicing safer sex for PLHIVs is probably hard in the long term [2]. In this regard, some studies found that different factors such as self-efficacy, responsibility, drug use, mental health and the context of the community that the PLHIVs are living should be considered as factors that can promote or demote positive prevention activities among PLHIVs [3].

2. POSITIVE HEALTH, DIGNITY AND PREVENTION

Positive prevention may be considered as an approach [4] or strategy [4, 5] or simply as a package of activities; but all of such definitions are similar in the fact that they focus on PLHIVs. According to the current literature, there was a misconception about the continuum and definition of positive prevention until 2008 [6]. In 2011, UNAIDS introduced a new framework for what we called

Positive Prevention as well as the Global Network of People Living with HIV [7]. The new term contains not only the concept of positive prevention, but also health and dignity and is "Positive Health, Dignity and Prevention". Positive Health, Dignity and Prevention (PHDP) covers a broader spectrum of policies and activities not only for PLHIVs but also for all of the members of a community, hence we all have responsibilities in the control HIV epidemic.

"Positive Health, Dignity and Prevention is not just a new name for the concept of HIV prevention for and by people living with HIV, formerly known as 'positive prevention'. Rather, Positive Health, Dignity and Prevention is built on a broader basis that includes improving and maintaining the dignity of the individual living with HIV, to support and enhance that individual's physical, mental, emotional and sexual health, and which, in turn, among other benefits, creates an enabling environment that will reduce the likelihood of new HIV infections".

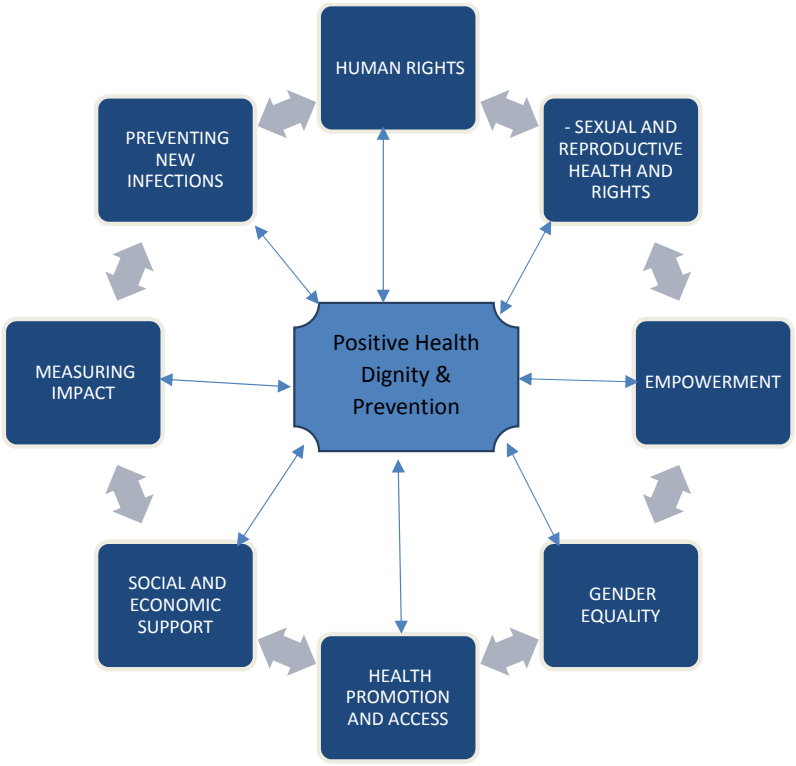

Fig. (1). Major components of Positive Health, Dignity and Prevention (PHDP).

CHAPTER 19

Management Model of Positive Clubs

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Abstract: Aiming the positive prevention, psychosocial support and reduction of stigma and discrimination, positive clubs have been established in Iran since 2006. We created a systematic management procedure using the Logical Framework Approach (LFA) and Work Breakdown Structure (WBS). Based on this model, a central council including trained people living with HIV (PLHIV) provides the management for positive clubs. Subsequently, under the supervision of this council, different practical committees are formed. These committees are in close interaction with each other and by participation of HIV positive and negative volunteers, we may anticipate the empowerment of people living with HIV as well as reduction of stigma and discrimination at the community level. The objective of this chapter is to discuss a conceptual model based on LFA and WBS in order to identify appropriate management and increase participation and empowerment of PLHIV in positive clubs. Challenges and recommendations of implementing this type of model for prevention efforts are also discussed.

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Keywords: Committees, Council, Discrimination, Logical framework approach, Model, People living with HIV, Positive club, Positive prevention, Psychosocial support, Stigma, Work breakdown structure.

1. INTRODUCTION

It would certainly be impossible to develop a successful national program to control HIV/AIDS without participation of People Living with HIV (PLHIV). Organizations of PLHIV are significant in the response to the global HIV/AIDS epidemic where by sufficient support, PLHIV may play a key role in the delivery of AIDS programs in their communities [1, 2]. The active participation of PLHIV empowers and urges the AIDS efforts further encouraging other people into action [1, 2]. Also, the Greater Involvement of People Living with AIDS (GIPA) in principle aims to enhance the quality and effectiveness of the AIDS response at the community and social level. Public involvement of PLHIV may break down the fear and prejudice and demonstrate that they may be productive members of the society [1, 3].

One of the most remarkable achievements in Iran is the establishment of positive clubs in 2006 under the supervision of relevant medical universities. Such clubs were designed to use community resources (non-governmental organizations) and the specialist, technical assistance of medical universities [2]. Objectives of positive clubs are positive prevention, psychosocial support with the aim of empowering and developing the capacities of PLHIV for the management and improvement of life skills as well as reduction of stigma and discrimination [4, 5]. The positive prevention is a collection of strategies which help PLHIV for adhering to healthier and longer lives. Thus, positive prevention is about maintaining the reproductive health, preventing sexually transmitted infections (STIs) and HIV infection progress in addition to increasing PLHIV responsibilities for prevention of HIV/AIDS [6]. Also, this approach strengthens the national response by mobilizing peer groups to promote the personal health of PLHIV, comply with treatment and prevention, fight stigma and social discrimination, and provide them with psychosocial support [6].

The objective of this chapter is to discuss a conceptual model based on Logical

Framework Approach (LFA) and Work Breakdown Structure (WBS) in order to identify appropriate management and increase participation and empowerment of PLHIV in positive clubs.

2. THE MODEL

We designed a unique method to address the issue of management of positive clubs including who should manage the positive clubs and the processes of implementing a positive club, outlined in Table **1**, Figs. (**1a** and **1b**). Supervisory tools are also outlined in Table **1**.

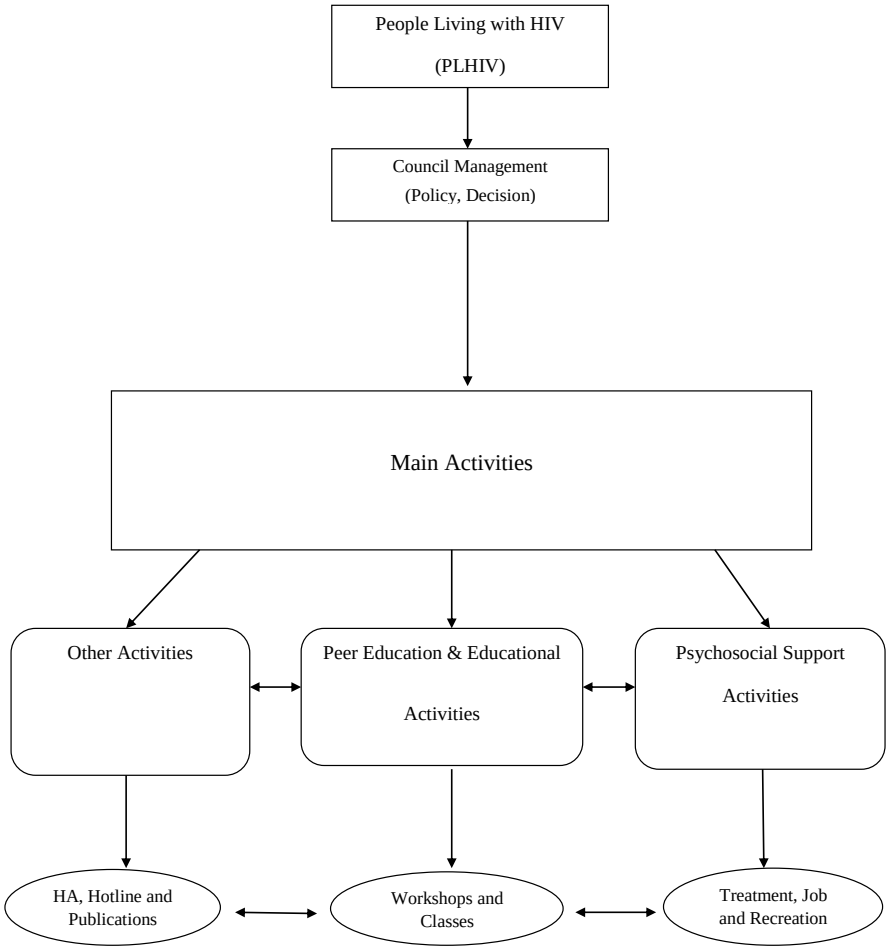

Fig. 1(a). Work Breakdown Structure (WBS) based on tasks.

CHAPTER 20

Integration of HIV Services into Primary Health Care (PHC) System

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Abstract: Various factors should be considered when deciding whether integration of HIV/AIDS services into Primary Health Care (PHC) would be beneficial or not. Many studies have stated the necessity of integrating HIV/AIDS programs and Sexually Transmitted Infections (STIs) in PHC and the positive impacts of this integration on a number of PHC goals; however, lack of a monitoring and evaluation (M&E) system makes it difficult to assess the efficiency of the integration into PHC. Considering the scale-up of care and treatment for HIV/AIDS in developing countries, there is increased debate that intensified attention to HIV programs may lead to declines in delivery of other PHC services.

Overall most evidences establish that integrated services can exert a positive effect on client satisfaction, leading to improved access to component services, and reduced HIV stigma, and also these are cost-effective. Key aspects of integration programs include: co-location of services, provision of effective substance use treatment, cross-training of care providers, and provision of enhanced monitoring of drug-drug interactions. Key components in implementing this agenda will be fostering the political tendency to

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fund infrastructure and service delivery, expanding street-level outreach services to injection drug users, and training community health workers able to cost effectively delivering these services.

Keywords: AIDS, Decentralization, HIV, Integration, Prevention, Primary Health Care (PHC), Service delivery, Stigma, Substance use, Treatment and Care.

1. INTRODUCTION

More than three decades ago, the world's Ministries of Health declared Primary Health Care (PHC), the delivery of basic preventive and curative services as "Health for all" a top priority at Alma-Ata. Since then, the world's poorest countries have not met most PHC goals [1]. Factors have included insufficient political prioritization of health, structural adjustment policies, poor governance, population growth, inadequate health systems, and scarce research and assessment on PHC [2].

Although HIV is one of the most important infectious cause of adult mortality in many countries of the world, AIDS prevention and care are not clearly ranking priorities for PHC, yet arguments occur among international health policy makers [1]. Therefore, inclusive strategies are required for effective delivery of preventive, diagnostic and curative services to these complex patient populations [3].

In this chapter, we discuss the integration of HIV/AIDS services into PHC, the benefits and pitfalls, and the world experiences.

2. BENEFITS OF INTEGRATION OF HIV/AIDS SERVICES IN PHC

Recently, the concern of integrating HIV services finds an increasingly high priority on public health agendas [1, 3]. HIV/AIDS has shifted to a chronic disorder and despite of disease causes, an integrated approach to the management of chronic diseases is needed in the PHC [4, 5]. The integration of HIV/AIDS programs into PHC has taken place in some countries around the world either partially or completely (Table **1**). However, the success of its implementation varies from country to country. Numerous factors come into play when deciding whether the integration of HIV/AIDS programs would be beneficial or not to a

region. Factors such as the careful monitoring of the government, community involvement, and skilled personnel have to a strong impact on the success of such programs [6]. An analytical approach is necessary to discover the potential barriers, adopt effective strategies for dealing with these barriers and to facilitate the integration. Generally speaking, the integration of such programs is a challenging topic that needs both appropriate funding and staff. Planning for HIV-related services depends on HIV prevalence in each country and the level of services differ from country to country and even differ between the different districts of a country. Countries, and even districts with a higher prevalence of HIV, should be provided with more services as well as more clinics than those with a lower prevalence. It is believed that the need for the integration is higher in developing countries because it has been shown that in such countries, HIV as well as Sexually Transmitted Infections (STIs) prevalence is higher than in developed countries [4, 5].

Table 1. An overview of different countries' status in providing the most important services regarding HIV/AIDS in Primary Health Care (PHC) System worldwide.

Country	Integration in PHC	Important services regarding HIV/AIDS	Centers providing services regarding HIV/AIDS	Consequences
Iran	Is not applied.	-Narcotics Anonymous (NA) -Providing programs for harm reduction (syringe and needle exchange, methadone therapy, condom distribution) -Providing HIV testing	-Voluntary counseling & Testing (VCT) centers -Positive clubs -Drop-in center (DIC)	-Increasing access to HIV testing -Become slow progression of the epidemic among injection drug users. -Control of HIV transmission through blood and its products were successful. -HIV Prevalence is low among the general population in the country.

CHAPTER 21

Community Involvement: New HIV Monitoring Strategies

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Abstract: HIV testing strategies should be carefully tailored to specific settings and populations. Screening algorithms typically include rapid test, ELISA and Western blot testing cascades. Over the counter consumer tests for oral fluids are expanding in developed countries, and early infant diagnosis screening programs such as Dried Blood Spot (DBS) testing are expanding in developing countries with high HIV prevalence. Advanced nucleic and PCR based testing platforms continue to be simplified as Point of Care (POC) equipment by numerous manufacturers. Psychosocial support and counseling are critical components of effective HIV testing programs in any community, and serve as a bridge between testing activities and early uptake to treatment regimens.

Keywords: DBS, EID, ELISA, Harm reduction, HIV testing, Oral fluid tests, Point of Care, Psychosocial support, Rapid tests, Serology, Western blot.

1. INTRODUCTION

Monitoring strategies for HIV are complex and require consideration of purpose, population, setting, technology, budgets as well as other factors. Groups for evaluation may range from patients, adolescents, infants, the general public, blood donors, sex workers, Injection Drug Users (IDU) to Sexually Transmitted Infections (STI) clinic attendees. The populations might have very specific

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characteristics, such as strict religious beliefs or varied educational backgrounds [1]. Settings for monitoring could be a hospital, a Voluntary Counseling and Testing (VCT) clinic, private homes in a door-to-door outreachservice, blood banks, urban settings, or very rural locations [2 - 4]. Technology and cost of screening tests continue to evolve and improve over time and require periodic reevaluations [5]. Studies may be undertaken to screen large numbers of patient samples, to confirm patients who previously were tested HIV positive, to monitor ART treatment, or to conduct an epidemiological survey. Monitoring may be driven by individual study as well, to assess viral loads or the emergence of drug resistance mutations. For any such endeavor, one needs to pay thoughtful attention to these, and other diverse issues. Even human subjects review committees and political factors can influence design of an appropriate HIV monitoring strategy [6 - 11].

2. TESTS FOR HIV INFECTION AND POINT OF CARE

Broadlyspeaking, HIV screening technologies typically are serologic tests, which detect antibodies specific to HIV, as well as more sophisticated Nucleic Acid Tests (NATs), which detect genetic particles of the HIV genome directly. More specifically, serologic assays may target antibodies in whole blood, plasma, dried blood spots, saliva or urine [12]. Detuned assays, which deliberately raise the detection limit of certain types of assays, can estimate the time of infection to examine HIV incidence [13]. NATs can provide qualitative infection information, or quantitative measurement of a patient's viral burden. Viral culture can characterize viral tropism and DNA sequencing can provide the HIV subtype information for patients.

Historically, first generation Enzyme Linked Immunosorbent Assays (ELISAs, viral lysate with IgG detection) emerged in the mid-1980s and was targeted toward high-risk populations. Improvements were driven by the need to reduce false positives as well as to screen for additional viral variants (various HIV-1 subtypes, HIV-2). Hemagglutination assays were followed by second (recombinant antigen) and third generation (IgG and IgM detection) ELISAs. The current fourth generation ELISA detects both HIV-1 and HIV-2 antibodies as well as p24 antigen. As with all HIV testing and screening, initial positive results by a

screening assay absolutely need to be confirmed by a second test before any result is reported to a patient [14]. Western blot confirmatory assays have largely been replaced by standardized NAT confirmatory testing in developed countries, and with secondary ELISA rapid test confirmation predominating in developing countries. Screening assays should be of high sensitivity, and the confirmatory test must have equal or higher specificity [5].

A milestone in HIV monitoring was passed with the US FDA approval of the over-the-counter OraQuick test kit in 2012 [15]. Designed for personal home use by the public, for a price under US$30 and the result in less thanone hour, the test can detect antibodies to HIV-1 and HIV-2 from a saliva sample. The manufacturer provides 24 hours telephone support in the US for technical assistance, and also can refer callers to social support networks. While the impact of this widespread testing capacity is still pending, enthusiasm runs high that this can expand early HIV screening and increase a much earlier access to care, particularly in marginalized populations less likely to see a physician on a regular basis [16]. However, testing in a medical setting still provides the best quality of care, and efforts to expand this capacity must be strengthened [17].

Routine oral fluid screening at dental office during exams is another new field of research [18]. The greatest burden of responsibility is perhaps the dental professional communicating sensitive information and acting in a counseling role. Blood bank screening remains an extremely important function at the community level, and the monitoring has evolved in this setting with technology such as gene chip arrays. In 1995 antibody testing of blood was expanded to include p24 antigen testing as well [19, 20]. Many countries worldwide now screen with fourth generation ELISA to reduce the number and cost of tests performed. The US FDA has recommended NAT testing of collected blood products and pooled screening is the current standard protocol of screening in this setting [21, 22].

With broad applications for developing countries and rural settings, point of care platforms for screening and testing have been expanding greatly in the past five years [23, 24]. CD4 testing platforms (Pointcare, PartecMiniPOC) are now available and viral load platforms continue to move toward improved versions [25]. Dried Blood Spot (DBS) collection and screening has become part of

CHAPTER 22

Monitoring and Evaluation of HIV/AIDS Interventions

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Abstract: Monitoring and evaluation is necessary for any program management endeavor however it has been a challenge for application to HIV/AIDS projects globally because of the multidisciplinary and multidimensional aspects of the epidemic. Results-based management has been the main driver behind monitoring and evaluation efforts with various methodologies and indicators used for different stages of the results chain. Complexity of the HIV/AIDS epidemic necessitates the use of triangulation approach and complexity science related methods in studying various HIV aspects from biology to social dynamics and policy-making. Participatory methods have also been utilized for enhancing trust, ownership and empowerment within affected communities. Some frameworks are introduced to help planning and implementing national monitoring and evaluation systems. The future of monitoring and evaluation could be more promising for ensuring accountability and scientific rigor.

Keywords: Accountability, Assessment, Effectiveness, Efficiency, Evaluation, Indicator, Monitoring, Participatory, Planning, Results, Triangulation.

1. INTRODUCTION

HIV/AIDS emerged as a public health concern in a world where evaluation science and practice was also developing rapidly. In fact, the complexity of biopsychosocial factors involved in HIV/AIDS epidemic was helpful in

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developing novel approaches for monitoring and evaluation of HIV/AIDS projects around the world."Increases in scrutiny, fierce competitions for decreased funding levels, strong demand for results, and great emphasis on accountability yielded higher pressure on non-profits and government organizations for providing the results, being accountable, demonstrating great performance, and acting like business users" [1].

HIV/AIDS program management and interventions dealing with the quality of life assessment in the target population and People Living with HIV (PLHIV), in particular, have generally faced the challenge for monitoring and evaluation (M&E) of projects and programs. The answers to the questions such as how certain practices would be proved to make different outcomes, whether a change is needed in programs, or whether there is an essential need for a new intervention, with some other questions in relation to accomplishment, effectiveness and accountability are provided through this process. When a state, for example, aims to make harm reduction policies, the M & E process will explain the pre-determined implementation of various components and services, like needle and syringe exchange, increasing used of condom, voluntary counseling and testing, and sentinel sites; and determine the levels of success in the strategies, individually and collectively, as the entire package.

The M&E is regarded as an applied research. The M&E seeks to improve decision-making process, develop knowledge with actions and problem-solving in health and social settings. According to The OECD, "Monitoring is defined as a continuous performance, applying systematic data collections on given indicators as to inform management and main stakeholders about ongoing projects with progress towards achievements, and utilization of allocated funds" [2]. Also, "Evaluation refers to a systematic and targeted evaluation of projects, programs, or strategies, in progress and completed, together with design, implementation, and outcome. The purpose is to demonstrate the extent of relevance and fulfillment of goals, efficiency, effectiveness, influence, and sustainability. Any evaluation should bring valid and useful knowledge, which allows the utilization of lessons learned for making decisions, whether of recipients or donors" [2].

On the other hand, the Results-Based Management (RBM) has changed the

traditional approach to M&E from measuring performance and outputs to assessment of outcomes and impact of health interventions. In RBM approach, a results chain or model is regarded as a manifestation of a program, defining how to achieve development goals (an aspect of the quality of human life). The approach covers causal associations and key assumptions for any level of results. This will be elaborated in details below.

Some experts prefer to integrate M&E in an inclusive frame to stress on a lifecycle approach in programming. Table **1** shows a framework with monitoring as a "process evaluation".

Table 1. Comprehensive evaluation framework.

Types of Evaluation	Broad Purpose	Main Questions Answered by it
Baseline Analysis / Formative Evaluation Research	Determines Concept and Design	Where are we now? Is an intervention needed? Who needs the intervention? How should the intervention be carried out?
Monitoring / Process Evaluation	Monitors Inputs and Outputs, Assesses Service Quality	How are we doing? To what extent are planned activities actually realized? How well are the services provided?
Effectiveness Evaluation	Assesses Outcome and Impact	How did we do? What outcomes are observed? What do the outcomes mean? Does the program make a difference?
Future plans / Cost-Effectiveness Analysis	Assesses Value-for-Resources Committed Including Sustainability Issues	Should program priorities be changed or expanded? To what extent should resources be reallocated? What are the next steps and needed resources?

2. INDICATORS FOR THE M&E FRAMEWORK

An indicator refers to a measure used to examine a condition, progress in a procedure, or results of an activity or project. There are a wide range of M&E indicators:

CHAPTER 23

Sampling Methods for Hidden Populations

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Abstract: In many countries access to some populations most at risk of contracting HIV is limited. Thus conventional sampling methods cannot be utilized for studying various aspects of the epidemic among those populations. Respondent-Driven Sampling (RDS) and Time-Location Sampling (TLS) methods are developed during the recent years to allow having more accurate and more generalizable estimates on the characteristics of the participants. RDS uses the links in the social network of participants for recruitment of new ones and TLS uses the places where the potential participants usually gather. Both methods have assumptions and limitations which should be considered when applying them to different groups and situations. Prior formative research may provide invaluable information on some factors which may influence the researchers' choice for using these methods including cost, time, feasibility and coverage of target population. This may also help in guiding development of public health interventions to mitigate the risks. Some statistical software is available for analysing data gathered from samples together with some modifications and tricks to decrease bias.

Keywords: Bias, Epidemic, HIV, Location, Population, Respondent, Risk, Sampling, Selection, Snowball.

1. INTRODUCTION

HIV/AIDS is associated with some high risk behaviours such as Injection Drug Use (IDU) and unprotected sex which in many societies impose stigma and discrimination to those committing them. The most at risk populations (MARPs)

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are usually hidden populations who are hard reached by health workers and researchers. Conducting a conventional survey with random sampling is not feasible through these groups because usually there is not a sampling frame available for them and they are usually a very small part of the general population, facing with stigma and discrimination. So simply doing a household survey cannot catch enough target participants. In the past decades, some efforts were deployed to find innovative approaches to overcome the problem of not having a representative sample. Two general strategies were used in this regard; using the links in the social network of participants and going to places where and when they are concentrated [1].

One of the earliest solutions was using snowball sampling in which a few selected participants function as seeds to invite other participants from their own social network. This process is replicated with the new participants until the desired sample size is achieved. In this way, convenient reaching of the sample size is achieved, however there are still some concerns which remain about non-random sample *e.g.* selection bias toward those who have a larger social network and might be at higher risk of HIV, but leaving the isolated individuals out of the sample. "Non-probability sampling methods such as snowball sampling are useful in formative research and in problem definition, but they are not suitable for producing data that can be confidently generalized to larger populations, although they are sometimes–incorrectly-used in this manner" [1].

2. RESPONDENT-DRIVEN SAMPLING

Respondent-driven sampling (RDS) was introduced in late 90's to minimize the bias in snowball sampling through a mathematical model which puts greater weight on the information received from "isolated" participants compared to those who have more connections [2]. In RDS the researchers select 5-10 seeds (or index cases) among target group who are well-connected to others and can recruit 2-4 other participants each. The recruitment is done through a fixed predetermined number of coupons or tickets which will be given to seeds and the new recruits. The cascade of new recruitment waves will continue until researches reach to the desired sample size or the stability of results among waves which is called "equilibrium". One of the main issues in RDS is following the chain of coupons

through coupon manager software. Also special softwares exist for statistical analysis of results.

There are three assumptions for an RDS study; 1) respondents know one another as members of the target population, 2) respondents' networks are linked and form a single network and 3) sample size is small relative to size of the target population. Lansky *et al.*, have proposed quantitative measures to evaluate, post-hoc, the extent to which the three assumptions were met [3].

An RDS sample is self-weighting only when two conditions are encountered: (1) network sizes for groups of analytic interest (*e.g.*, gender, race) are equivalent, and (2) efficacy of recruit are equal between groups. Unfortunately these two conditions are not met usually, so post-stratification weights are required to yield population estimates that control for these sources of bias [4].

Goel and Sharad have argued that having a greater sample size in RDS does not necessarily lead to more accurate estimates and suggested reduction of recruitment coupons for each participant [5]. They also showed that bottlenecks, anywhere in the network, impact the quality of RDS estimates [5].

"Two main estimation methods are generally used. The RDS-1 estimator, currently in wide use, can be implemented with the standard respondent-driven sampling analysis software. RDS-1 accounts for patterns of recruitment between subgroups and the average number of other members of the target group who the recruiters know (the "network size") in each subgroup. RDS-2 is a more recently developed estimator that relates respondent-driven sampling estimation to widely used survey estimation through the use of a generalized Horvitz–Thompson estimator. RDS-2 accounts for network size only. Initial theoretical analysis has asserted that the RDS-2 estimator is asymptotically unbiased as long as six key assumptions are met, including that respondents accurately report the size of their "network" (the number of other members of the target group they know), that respondents randomly recruit from their network, and that respondents have reciprocal relationships with members of the target population" [6]. RDS data are usually analysed with RDSAT software which generates appropriately weighted estimated proportions with confidence intervals. However RDSAT software is not

CHAPTER 24

Recent Researches on HIV/AIDS

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Abstract: Despite the publication of many papers on the HIV/AIDS field, the central topics and subjects of research is not clearly determined yet. Therefore, in this chapter we aimed to present the information that may be guide researchers in the field of HIV/AIDS. In order to find the most common studied topics we searched for the related keywords in PubMed and Science-direct. This chapter presents the results of a review of all articles that were published in these databases.

Moreover, we selected the top three journals and studied their most recent issues. All articles published in these journals were classified in view of their subjects, so that to identify and determine the current important topics in the field of HIV/AIDS all over the world; additionally, we tried to list about two percent of all articles which contained HIV/AIDS as their keywords and have been published in PubMed so far. Overall, 4.2% of all articles which were published in Science-direct-indexed journals contained HIV/AIDS as keywords in their titles. The most common and important studied topics include the followings: epidemiology and social topics, cure and antiretroviral therapy, co-morbidity in HIV/AIDS, virology and serology, and HIV/AIDS and cancer.

Epidemiology of HIV/AIDS is still the most frequent topic of research. Most of the reviewed studies were carried out in this field; however, as we found HIV/AIDS treatment planning was also among the most important studied topics. In addition, according to our findings, clinical trials have been increasingly utilized as a research method in the last 10 years.

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1. INTRODUCTION

Thirty years is not a long time in the history of adisease. However, the past three decades have seen the most intensive investigations and research in to HIV/AIDS compared to any disease known to mankind [1, 2]. New articles are published daily on HIV and AIDS. The most common topics include HIV/AIDS news, antiretroviral therapy (ART), awareness, preventive measures, treatment options, and co-infections such as tuberculosis in HIV [2, 3]. Each step forward in the advance against HIV brings us to a crossroad, a point where a decision isneeded about the direction in which to proceed. ART is well established as an important tool for treatment and prevention; however, it is very likely that the provision of ART for 34 million people is unsustainable in the long term. In 30 years we have gone from warnings of the black plague, even in reputable publications, to advocating thereal possibility of eradication [1]. According to WHO reports on 2013, ischemic heart disease, stroke, lower respiratory infections, chronic obstructive lung disease, diarrhea and HIV/AIDS have remained the top major causes of deaths during the past decade. HIV/AIDS is the sixth cause of death in the world up to now; the disease is ranked differently in different countries with disparate incomes. The graphs show that in low-income countries HIV/AIDS is more important and is the second cause of death while in high-income countries HIV/AIDS is not among the 10 top causes of death [4].

Conducting a research always begins with a statement of a problem. Finding a problem therefore is not difficult, but identifying one for the purpose of research is not always easy. One of the most important primary tasks of research is to identify and clearly define the problem you wish to study [5]. Despite all the available resources, the appropriate areas to research for researchers have not been determined [5 - 7]. Therefore, we aim to present the information that may be useful for active researchers in the area of HIV/AIDS in the following section.

2. METHODS

There are many important databases of medical science such as PubMed, SCIENCEDIRECT, OVID, SPRINGER, and ISI. We screened PubMed and

Science-direct for our search. Thus this reportis based on a review of all articles that were published in these databases from November 2003 to November 2013. We carried out this review by searching AIDS OR HIV as keywords. The results, then, were classified based on time, place, method, type of article, and important subjects. The collected information was organized into tables. In addition, we studied ISI-indexed journals which were selected based on subject and the relevance to our searching terms. Afterward, they were classified based on their recent impact factor. We found top 10 journals that are focused on HIV/AIDS subject. We selected the top three journals and studied the most recent issues. All articles published in these journals were sorted according to subject in order to conclude the current important topics in the field all over the world. Besides, we searched AIDS or HIV in these databases, then studied the most recent 100 articles that were sorted by publication time, and classified these articles based on the subject to find the most important topics too. Our search results are presented in tables in results section.

3. RESULTS

Some tables are presented below which were designed to indicate the current most common topics of study about HIV/AIDS. Studying this information may help scholars to find a problem to start a research. All results were obtained in November 2013(Table **1**).

Table 1. The frequency of HIV/AIDS related articles published in journals indexed in PubMed and Elsevier databases in the last five and 10 years, from beginning up to now and in-press articles in different databases.

No.	Keywords	Database	Total search result	Articles published in last 10 years	Articles published in last 5 years
1	HIV	PubMed	261,958	125,973	67,928
2	HIV	Elsevier	232,404	138,558	84889
3	AIDS	PubMed	216,382	74,943	38,418
4	AIDS	Elsevier	280,206	126,835	76,500

We searched title field for the keywords of HIVand AIDS in PubMed database and we found 13839 articles from which 100 most recent articles were studied and

SUBJECT INDEX

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SEYEDAHMAD SEYEDALINAGHI

I attained my MD degree from Tehran University of Medical Sciences (1998-2006) with an A-grade. As a brilliant student, I received letters of commendation from the university and exemplary Intern in the Infectious ward of Imam Khomeini Hospital and Bahrami Pediatric Hospital in 2006. I have been honored to attend Iran's National Razi Festival on Medical Science since 2009 and was awarded in 2011 and 2012.

As a researcher, I have been working with the Iranian Research Center for HIV/AIDS (IRCHA) since 2006. I followed the M.Phil course with A-grade after my first degree and I am currently a PhD candidate in biomedical research at Tehran University of Medical Sciences. Moreover, I have written a total of 103 articles and ten scientific books, mainly focused on different aspects of HIV/AIDS. Further, I spent a variety of professional training courses related to HIV/AIDS in Iran and abroad.

My appointments were as the followings:

- UNAIDS Representative of IRCHA in Iran
- Manager of Tehran Positive Club. The Club delivers diverse support services to People Living with HIV and it was also nominated for the Red Ribbon Award in 2010, 2012, 2014 and 2016 from Iran
- Reviewer of Iranian Journal of Public Health, Journal of School of Public Health and Institute of Public Health Research and Asian Pacific Journal of Tropical Biomedicine
- Member of Iran's Authors, Journalists, and Artists Support Credit Fund
- Member of Technical Committee of Iranian Ministry of Health and Medical Education for preparing "Global AIDS Response Progress Reporting" in 2012 and 2014.
- Member of National Steering Committee of HIV/Tuberculosis active case finding in Health and Treatment Office of Iranian Prisons Organization.