Review Article

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http://www.imedpub.com

Translational Biomedicine
ISSN 2172-0479

2015
Vol. 6 No. 4: 28

DOI: 10.21767/2172-0479.100028

HIV in Intensive Care Unit: Concerns and Constraints of Intensivists

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Citation: Kar SK. HIV in Intensive Care Unit: Concerns and Constraints of Intensivists. Transl Biomed. 2015, 6:4.

Abstract

The increasing prevalence of HIV (human immunodeficiency virus) infection in recent times has led to increasing exposure, and the possibility of nosocomial transmission of HIV. The present day scenario highlights the need for intensivists to enforce strict adherence to infection control protocol at site when working in ICU. Thus strict adherence to Standard precautions when handling body fluids especially hand washing, proper management of accidental needle-stick injury and scientific disposal of biomedical waste along with current PEP guidelines are of paramount importance. In the HAART era, though hospitalisation of HIV infected patients has significantly decreased, but the rate of ICU admissions is still high. HIV patients may be admitted to ICU for many reasons, of which acute respiratory failure as a result of opportunistic infections accounts for approximately 25-50%. Today, HIV patients are being admitted to the ICU for medical and surgical causes unrelated to their HIV infection, such as malignancies, pacemaker implant, liver and renal diseases, minimal invasive surgeries like laparoscopic ones, orthopaedic surgeries for fractures and implants, brain surgery for road traffic accident injury are only a few. The number of persons living with HIV/AIDS (PLWHA) has increased and critical care specialists may be more likely to admit more HIV patients to the ICU and pursue aggressive life-support measures. But for resource constrained countries, where population and ICU bed ratio are abysmally low, decisions for admission in ICU by critical care specialists are often made in the absence of explicit policies and guidelines. Global and national commitments are required, providing proper HIV treatment and prophylaxis without discrimination and maintaining accountability and code of ethics.

Keywords: HIV; ICU; Standard precautions; Post exposure prophylaxis

Received: September 24, 2015; **Accepted:** December 04, 2015; **Published:** December 10, 2015

Introduction

AIDS was first recognized in the United States in 1981, by the U.S. Center for Disease Control and Prevention, Atlanta Georgia (CDC), although the period of silent spread actually began years earlier since 1971 [1]. In 1983, Luc Montagnier at Pasteur institute, Paris had found evidence of a retrovirus in a patient with lymphadenopathy (PGL), and they could distinguish it from HTLV-1 and thus Human Immunodeficiency Virus (HIV) was first isolated [2]. Robert Gallo in 1984 isolated HIV from 48 homosexual patients suffering from Pneumocystis jirovecii pneumonia (PCP) and kaposis sarcoma and which was later unambigously demonstrated to be the causative agent of AIDS [3]. Thirty years on, HIV pandemic has reached alarming proportions. According to United Nations AIDS (UNAIDS) in 2014, 36.9 million people were living with HIV and they continue to increase, because more people globally are accessing antiretroviral therapy and as a result are living longer and healthier lives [4]. According to report in June 2015, 15.8 million people were accessing treatment [4]. In 2014, around 2 million people were newly infected with HIV and 1.2 million people died of AIDS-related illnesses [4]. The increased prevalence of HIV infection is reflected in the increase of promiscuous sexual intercourse, and the possibility of nosocomial transmission of HIV highlights the need for intensivists and to enforce rigorous infection control policies to protect themselves, other healthcare providers and their patients. Hence management of HIV infected patients pose a significant challenge for healthcare providers at the time of surgery, in obstetric management, in the realms of

orthopaedics, trauma surgery, cancer surgery and specially in the setting of intensive care. In this review, we attempt to highlight recent insights and advances that have been made in relation to HIV treatment and prevention policies with special emphasis to ICU.

Epidemiology and pathogenesis

HIV belongs to family of Retroviridae and the genus Lentiviridae. These are cytopathic (cell damaging), have a long latent period and a chronic course [5]. Two distinct variants of HIV have been identified: HIV-1 and HIV-2. HIV is a highly mutable virus and molecular analysis shows diversity over all regions of viral genome. HIV-1 has three groups: HIV-1 group M (Major) which is responsible for 90% infection worldwide, followed by HIV-1 group O (Outlier) and only few cases are reported for infection with HIV-1 group N (New) [5]. HIV-2 is less virulent, rarely causes full-blown AIDS and does not spread as widely and rapidly like HIV-1.

HIV has got tropism for CD4 expressing cells. HIV infects and destroys helper T cells and other CD4+ cells leading to a number of immunological deficiencies [5]. Retroviruses contain the enzyme reverse transcriptase. After fusion of the virus with host cell membrane, genome is uncoated and internalised into the cytoplasm. The viral reverse transcriptase catalyses the reverse transcription of the genomic RNA into doubled stranded DNA which is integrated into the host cell genome by viral integrase enzyme. This proviral DNA transcribes from time to time with production of complete virus particles capable of infecting other CD4+T lymphocytes leading to cell death and immunodeficiency, opportunistic infections and malignancies. Approximately 10^{11} new viral particles are produced every day and 10^{9} CD4+T lymphocytes die each day. Eventually there is profound loss of CD4+T cells with reduction in their number and normal CD4:CD8 ratio is reversed. Though major damaging effect is on cellular immunity, humoral immunity is also affected finally leading to AIDS.

Two major classification systems on HIV diseases are currently in use: the U.S. Centers for Disease Control and Prevention (CDC) classification system [6] and the World Health Organization (WHO) Clinical Staging and Disease Classification System [7]. The CDC disease staging system (most recently revised in 1993) assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms. In contrast to the CDC system, the WHO Clinical Staging and Disease Classification System (revised in 2007) [7] is based on clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods. The full blown AIDS patients with opportunistic infections may require intensive care due to several disease complications including malignancy.

Causes for ICU admissions among HIV infected patients in HAART era

HIV patients may be admitted to ICU for many reasons. Acute respiratory failure as a result of opportunistic infections accounts for approximately 25-50% of intensive care unit (ICU) admissions in HIV-infected patients [8]. Most commonly it is secondary to *Pneumocystis jiroveci* pneumonia (PCP) and bacterial pneumonia (BP) (*Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus* and *Pseudomonas aeruginosa*), followed by aspergillosis, herpetic infections, oral and pharyngeal candidiasis and cytomegaloviral (CMV) pneumonia, Mycobacterial infections (*Mycobacterium tuberculosis* and atypical organisms, e.g. M. avium intracellulare) [8-11]. Other common indications for ICU admission are sepsis and central nervous system (CNS) dysfunction and complications due to Cryptococcal and Candidal meningitis, Subacute encephalitis, Herpes simplex encephalitis, multifocal leukoencephalopathy [10,11]. Lesser common causes are for gastrointestinal (GI) bleeding due to ulceration by infection or Kaposis sarcoma and for cardiovascular disease by opportunistic bacterial infections causing endocarditis and/or congestive cardiac failure. The spectrum of diseases requiring ICU admission is changing in the setting of HAART. In HAART era, hospitalisation of HIV infected patients has significantly decreased, but the rate of ICU admissions has not [11-16]. The reasons are, it has been seen that about 25-40% of HIV-infected patients were not known to be positive at the time of ICU admission [11,16]. Secondly around 50% of patients usually were not found to be on effective HAART during admission [11,16]. Most importantly, number of persons living with HIV has increased as overall survival improved because of effective HAART. So more number of patients living with HIV, is likely to get admitted in ICU to pursue aggressive life-support measures [15,16]. So, many are being admitted to ICU for medical and surgical causes unrelated to their HIV infection [10,11] such as trauma, post-operative care, asthma, renal failure, liver diseases and surgical causes [10,13,14]. In a study from France, the proportion of admission for non-AIDS-related conditions increased substantially from 42% to 63% when comparing admissions between 1995-1996 and 1997-1999 [11]. Also in New York City, ICU admissions for non-HIV-related disease increased substantially from 12% in 1991-1992 to 67% of all admissions in 2001 [12]. Liver disease due to coinfection with hepatitis C with HIV is increasing as a cause of death, [13,14] and complications related to cirrhosis often require ICU admission. European and American studies showed approximately 5-12% of hospital admissions for HIV-infected patients need ICU care [15,16]. But for resource constrained countries, where population and ICU bed ratio is very poor, these decisions for admission in ICU by critical care specialists are often made in the absence of explicit policies and guidelines, which may be subject to bias.

Modes of nosocomial transmission of HIV

HIV has been isolated from blood, semen, vaginal secretions, and other body fluids like cerebrospinal (CSF), synovial, pleural, peritoneal, pericardial, amniotic, and breast milk. Modes of transmission are oral, rectal and vaginal intercourse, blood product transfusion, shared intravenous needles, occupational acquisition and vertical transmission from mother to child. Possible modes of nosocomial transmission of HIV in ICU may occur from patient to intensivist, from patient to patient, or from intensivist to patient. HIV can be transmitted from the infected patient to the intensivist as a result of exposure to infected blood and body fluids. This can occur either through a sharp injury or small or large volume splash on mucus membrane or broken skin. Deep subcutaneous or intramuscular exposure to a blood-contaminated hollow needle from a patient with high HIV viraemia is the worst type of contact. Most contaminated percutaneous

injuries occur during multistep procedures, during recapping of needles or when contaminated sharps are not discarded safely [17]. A single needlestick injury with HIV infected blood may be associated with a 0.31% risk of HIV transmission [18]. Lack of proper infection control practice and use of personal protective equipments (PPE) among the intensivists have put them at risk. A needlestick injury through one pair of gloves has been associated with a 10-100-fold reduction in the inoculum [19]. A second pair of gloves would give additional benefit [20].

Patient to patient nosocomial transmission occurs by use of a common syringe during drug delivery on a large scale for several patients. Also contaminated anaesthetic equipment is a potential route of HIV transmission. Airway management devices are often reused between patients in resource limiting conditions. In one study, out of 65 laryngoscope blades and handles ready for use, 26 (40%) were found to be contaminated with occult blood due to lack of proper cleansing and disinfection [21].

Intensivist to patient transmission rarely occurs following injury to intensivist resulting in bleeding, contaminating instruments and their contact with patients.

Increased demand for ICU care of HIV patients, changing outcome and factors affecting ICU outcome

The spectrum and outcome of critical illness in HIV patients is changing in the setting of highly active antiretroviral therapy (HAART). As the overall survival has improved in HIV-infected patients on HAART, the number of persons living with HIV has increased and critical care specialists may be more likely to admit patients to the ICU and pursue aggressive life-support measures [22]. At the beginning of HAART therapy (1990 and 1996), the early ICU mortality was not changed or moderately improved and was 20.6% in 1990-92, 27% in 1995-96 and 25% in 1998-2000 [11,16] Whereas 6-month ICU mortality improved dramatically from 49% in 1990-92, to 38% in 1995-96 up to 30% in 1998-2000 [11,16].

Mechanically ventilated HIV patients are twice as likely to die in the ICU compared to non-HIV patients [23]. The need for invasive mechanical ventilation and duration of ventilation remains a predictor of ICU and hospital mortality in this group [24]. The reported in-hospital mortality for AIDS patients admitted to the ICU is approximately 25-40%, with a median ICU length of stay of 5-11 days [9,10,11,16]. The highest mortality rates for HIV patients requiring ICU admission are associated with sepsis and respiratory failure, especially if due to PCP, mortality rates remain as high as 50-68%, [25] for CNS dysfunction mortality rate is 20-48%, [25] for GI disease is approximately 30-35% [9,10]. However, patients admitted with non-HIV-related conditions may have better outcome and 3.7 times longer survival according to a study [10]. Predictors of increased hospital mortality include need for mechanical ventilation and disease severity (as assessed by scoring systems such as the Simplified Acute Physiology Score I [SAPS I] and the Acute Physiology and Chronic Health Evaluation II [APACHE II] score) [11,25]. The CD4 T-cell count and the HIV RNA level are predictors for long-term mortality after ICU admission but generally have not been predictive of short-term mortality during ICU stay [10,24].

ICU dilemmas faced by intensivists in resource constrained setting

No clear evidence based guidelines are available to assist the intensivist in deciding which patients are to be admitted to ICU, particularly in the context of HIV infection in a resource-constrained environment [26]. Each country has a professional association that guides and regulates ethical conduct, particularly with regard to people living with HIV/AIDS (PLWHA). These guidelines protect PLWHA against stigmatisation and discrimination by health professionals, particularly with regard to access to healthcare, treatment and support programmes. The major limitation lies in number of ICU beds available and is disproportionately low in certain developing countries like India, where population : ICU bed ratio is 1:14,000, compared to USA the ratio is 1: 400. So ICU beds become inaccessible and unaffordable to many citizens.

Monitoring and treatment of HIV patients in ICU

The question is whether critically ill HIV patients who require ICU admission for AIDS-related conditions should continue ART or stop the drugs while in the ICU. This can be answered definitively only by a randomized, prospective study which is still inconclusive. Two retrospective studies conducted at San Francisco General Hospital on all HIV-infected patients admitted to the ICU between 1996 and 1999, and between 1996 and mid-2001, suggest that ART may improve outcomes in critically ill HIV patients [10,27]. But intensivists should be aware of several complicating issues in patients who are already on ART or who initiate ART in the ICU. The antiretroviral agents are available as oral tablets and suspensions, except for Zidovudine and Enfuvirtide which are available in parenteral form. So, in severely ill patients, due to unpredictable gastrointestinal absorption, there are chances of potential drug interactions. Second, protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized by the cytochrome p-450 enzyme system, altering the metabolism of other drugs metabolized by cytochrome p-450 enzyme, hence are involved in numerous drug-drug interactions that can alter serum drug levels and result in adverse effects [28]. This can produce both drug toxicities due to increase in serum levels of drugs or lack of efficacy if drug levels are reduced. Third issue is for ART, even a few days of suboptimal levels of drugs due to poor absorption or pharmacokinetic interactions can lead to irreversible drug resistance. Thus, in most situations, the best strategy is to stop all ART during the ICU admission, and to consult an experienced pharmacokineticist about the effects on drug metabolism even after ART has been stopped [28]. Stopping ART is unlikely to lead to drug resistance. Fourth issue is patients on ART may experience worsening of a previously recognized or unrecognized underlying opportunistic infection, such as cryptococcosis, tuberculosis, or PCP, because of immune reconstitution syndromes which can be life threatening. Also patients may develop drug hypersensitivity reactions. So whether to continue ART or not is a very critical decision for intensivists.

General infection control

Intensivists and health care providers must take appropriate preventive steps to reduce the likelihood of occupational HIV

transmission. Approximately 20% of all patients with HIV infection undergo surgery and invasive procedures like, lymph node biopsy, splenectomy, partial colectomy, placement of central venous lines, gastrostomy tubes, and diagnostic procedures at some time during the course of their illness. There is no justification to withhold surgical intervention on the grounds of HIV infection alone as it is not associated with an increased postoperative risk of death or complications up to 30 days after the procedure [29]. Hence to prevent nosocomial transmission of HIV to intensivists, general infection control measures and standard precautions [30] to be followed according to latest guidelines available. They apply to blood, body fluids containing blood, semen, vaginal secretions, tissues, CSF, pleural, peritoneal, pericardial and amniotic fluids. They do not apply to faeces, sputum, sweat, tears, urine and vomitus unless they contain blood.

Hand hygiene: The term "hand hygiene" includes both handwashing with antiseptic-containing soap and water, and use of alcohol-based products (gels, rinses, foams) that do not require the use of water. In the absence of visible soiling of hands, approved alcohol- based products for hand disinfection are preferred because of their superior microbicidal activity, reduced drying of the skin, and convenience. Hand hygiene is essential element of Standard Precautions that reduces the transmission of HIV and other infectious agents in healthcare settings.

Personal protective equipments (PPE): PPE refers to a variety of barriers and respirators used alone or in combination to protect mucous membranes, airways, skin, and clothing from contact with HIV and other infectious agents. Guidance on the use of PPE and procedure for donning and removing PPE has been detailed in 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings by CDC and Healthcare Infection Control Practices Advisory Committee. [30] Disposable or reusable PPE should be placed in designated container in a location that is convenient to facilitate disposal and containment of contaminated materials. Hand hygiene is always the final step after removing and disposing of PPE.

Gloves

During non-surgical patient care, a single pair of gloves generally provides adequate barrier protection. Nonsterile disposable medical gloves made of latex or nitrile are preferred for routine patient care and clinical procedures. When gloves are worn in combination with other PPE, they are put on last.

Isolation gowns

Impervious isolation gowns are used to protect the care giver's arms and exposed body areas and prevent contamination of clothing with infected materials. Gowns are usually the first piece of PPE to be donned and they should be removed before leaving the patient's room to prevent transmission.

Face protection- masks, goggles, face shields

The mucous membranes of the mouth, nose, and eyes are susceptible portals of entry for HIV. Procedures that generate splashes or sprays of blood, body fluids, secretions, or excretions (e.g., endotracheal suctioning, bronchoscopy, invasive vascular procedures) require either a face shield or mask and goggles. Face shields extending from chin to crown provide better face and eye protection from splashes and sprays.

Respiratory protection

CDC currently recommends N95 or higher level respirators for personnel exposed to patients with suspected or confirmed tuberculosis co-infection with HIV.

Foot wear

Gumboot types of footwear are to be worn to avoid little cuts and abrasions of feet being contaminated by body fluids.

Safe work practices to prevent exposure to bloodborne pathogens:

Needlesticks and other sharps-related injuries can be prevented by following safe injection practise, which includes**:**

- Use of disposable single use needle and syringe.
- Re-capping and re-sheathing must be avoided.
- Needles are cut at hub (to prevent recycling) by needle cutter/ shredder and not by electric needle burner (risk of spurting of blood and infectious material). Dispose sharps and needles in rigid, puncture proof container containing 1% hypochlorite after a contact time of at least 30 minutes. The puncture-proof container should always be at point of use to avoid the temptation of re-capping.
- Use PPE such as gloves, mask and goggles which are appropriate during the procedures. Cleaning of contaminated surfaces or equipments and disinfection and sterilisation of instruments with proper disinfectant and safe handling and disposal of contaminated material are essential precautions to prevent HIV transmission. Manual cleaning of the endoscope with detergent eradicates >99% of the HIV virus from the instrument, and subsequent high level disinfection with 2% glutaraldehyde for 20 minutes can completely eliminate the virus from endoscopes and other metal instruments [31,32].

Blood spillage management

HIV is rapidly inactivated after being exposed to commonly used chemical germicides at much lower concentrations than that used in practice. Before cleaning the spill, wearing of gloves and other personal protective equipment is a must. Any absorbant material is to be placed over the spill and the surface to be cleaned to remove organic material. If the surface is nonporous, 1% sodium hypochlorite solution is used (e.g., household bleach in 1:100 dilution) and if the surface is porous 10% sodium hypochlorite solution is used (e.g., household bleach 1:10 dilution) and applied for 20-30 minutes for decontamination, followed by thorough cleaning of the area. The absorbent material should be further disinfected in sodium hypochlorite solution before final disposal [33].

Needle stick injury management and post exposure prophylaxis

Taking care of the wound immediately after the accident by washing thoroughly with soap and water is of utmost importance. In case of contact with mucous membranes, water or a saline solution is used and never alcohol. No evidence of extra benefit

with application of antiseptics or disinfectants has been found. It is important to report the incident immediately to the department and employer with proper registration and ensure subsequent management and appropriate follow up care. Assessment of infection risk like type of exposure and status of source person, while maintaining confidentiality of the source should be done for proper post exposure prophylaxis (PEP). Needle stick injury is regarded as an urgent medical concern and PEP should be started as soon as possible within 72 hours. If the source person has a negative HIV antibody test, PEP is stopped.

According to 'Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach' disseminated as a printed publication by WHO and electronically on the WHO website on December 2014 as 'Supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection' the new recommendations for PEP are as in **Table 1**.

In contrast to the 2007 WHO guidelines for PEP, these guidelines consider all types of exposure and provide recommendations for all populations with no distinction between occupational and non-occupational exposure and the same drug regimen should be prescribed irrespective of exposure and source code. It also provides recommendations for the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. Co-trimoxazole prevents and treats a variety of bacterial, fungal and protozoan infections. These updated recommendations have expanded the use of co-trimoxazole for all populations, at any CD4 threshold and for a longer duration, for preventing HIV-related opportunistic infections but also for the preventive benefit of reducing mortality and morbidity from severe bacterial and malaria infections among adults, adolescents and children living in resource-limited settings.

Conclusions

HIV-infected patient who requires ICU admission should have easy access to such level of care. For this there should be comprehensive legislation for each country addressing HIV/AIDS and criteria for ICU admission. Also availability of ICU beds should be increased in both private and public hospitals. When there is no ICU admission policy, sometimes HIV status may be commonly used as an ICU exclusion criterion, rendering such decision-

Table 1 Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children (WHO 2014).

An HIV post-exposure prophylaxis regimen with two antiretroviral drugs is effective, but three drugs are preferred.
Preferred antiretroviral regimen for adults and adolescents
TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV postexposure prophylaxis among adults and adolescents. LPV/r or ATV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis among adults and adolescents. Where available, RAL, DRV/r or EFV can be considered as alternative options.
Preferred antiretroviral regimen for children ≤10 years old
AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis among children 10 years and younger. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens. LPV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis among children younger than 10 years. An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV and NVP.
Prescribing frequency
A 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment.
The use of co-trimoxazole prophylaxis for HIV-related infections:
Among adults including pregnant women:
Co-trimoxazole prophylaxis is recommended for severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or for a CD4 count ≤350 cells/mm3. • In settings where malaria and/or severe bacterial infections are highly prevalent, cotrimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.
Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV infection who are clinically stable on antiretroviral therapy, with evidence of immune recovery and viral suppression.
Infants, children and adolescents:
Co-trimoxazole prophylaxis is recommended for infants, children, and adolescents with HIV, irrespective of clinical and immune conditions. • In settings with a high prevalence of malaria and/or severe bacterial infections, co-trimoxazole prophylaxis should be continued until adulthood irrespective of antiretroviral therapy provision. • In settings with low prevalence for both malaria and bacterial infections, cotrimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virally suppressed on antiretroviral therapy for at least 6 months and CD4 >350 cells/mm3.
HIV and TB coinfection:
Routine co-trimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts.

TDF: Tenofovir Disoproxil Fumarate; 3TC: Lamivudine; FTC: Emtricitabine; LPV/r: Lopinavir/Ritonavir; ATV/r: Atazanavir/Ritonavir; RAL: Raltegravir; DRV/r: Darunavir/Ritonavir; EFV: Efavirenz; AZT: Zidovudine; ABC: Abacavir; NVP: Nevirapine.

making irrational. Global and national commitments require providing HIV treatment and prevention to everyone in need, following the human rights principles of non-discrimination, accountability and participation.

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