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Personalized Medicine for HIV Control: A Systematic Review Study

Shekoofeh Farahmandpour[1], Nastaran Dehghani[1], Asra Khalkhalizadeh[1], Paniz Hajihossein[1], Armin Nikdehqan[1*]

[1] Department of Biology, Faculty of Basic Sciences, Islamic Azad University, East Tehran Branch, Tehran, Iran.

**Corresponding author: Armin Nikdehqan, Department of Biology, Faculty of Basic Sciences, Islamic Azad University, East Tehran Branch, Tehran, Iran. Email: a.nikdehqan@yahoo.com.*

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Abstract:
There were more than thirty-eight million HIV infections worldwide. Combination antiretroviral therapy (cART) has progressed to the point where invisible viral loads are now feasible, and HIV carriers frequently lead almost everyday lives with considerably greater average life expectancies than in the past. However, there is still no cure for the disease. Even though the ailment usually advances to a chronic state, an individual's unique course of progression may differ significantly from the average and manifest distinctively for each patient. This diversity begs whether a typical treatment strategy is appropriate for a patient.

INTRODUCTION

AIDS is an illness that presents its victims with various issues (1). Human Immunodeficiency Virus (HIV) is the disease's primary causal agent (2). HIV severely harms the immune system. After this virus was discovered in the United States, the illness has transformed throughout the last several decades and is now spreading over the whole globe (3). A kind of T-lymphocyte cell called CD4 is damaged and destroyed by HIV because CD4 cell density in a healthy person's body ranges from 500 to 1500 cells per cubic meter but fewer than 200 in a person with the illness (4, 69). This harm accumulates over time and results in various illnesses in the patient, including cancer (5).

It is possible to mention bodily fluids, including blood, semen, vaginal secretions, and breast milk, as possible transmission routes for this illness(6). Lymph nodes that are enlarged, exhaustion, frequent fevers, headaches and other bodily pains, vomiting and nausea, weight gain, diarrhoea, vaginal and oral infections, pneumonia, and shingles are all signs of the chronic stage of HIV(7). Given that HIV affects a person's DNA, this illness is incurable, and there is no cure for its causes (8). However, efforts have been made to control this illness, and the only effective treatment is the use of antiviral medications that a doctor prescribes (9). If the illness is not controlled, the patient will contract AIDS, and their body will not be able to fight infectious diseases (10). Consequently, it makes a person more susceptible to illnesses like meningitis, oral thrush, and cytomegalovirus (11).

Because there is no treatment for this illness, it is best to follow the adage "prevention is better than cure" and practice good hygiene to avoid contracting HIV(12). For everyone to be aware of this illness and to pay greater attention to their health, the best course of action is to educate the public, particularly teens, about HIV and how this disease is spread. A person-centred medical approach may find the finest answers in this area (13).

Most HIV transmission routes have much to do with lifestyle, personal habits, and behaviors. For instance, using drugs, smoking, or engaging in unhealthful sexual behavior raise the risk of contracting the illness (14). Even though these habits are daily in specific groups and nations, they may be changed with the proper guidance and instruction (15). So, utilizing prescription medication may help to avoid this sickness. Uganda and Thailand are two nations that have succeeded in lowering the pace of the spread of this illness following the principles of personal medicine (16).

Lack of preventive and poor personal hygiene will lead to disorder in society and personal life. Individual health first ensures one's health, then the health of other family members, and lastly, in the second stage, the health of whole communities (17). It should not be overlooked that maintaining personal hygiene and health, including vaccination, altering habits and behaviours, and being aware of the hazards of HIV, may be managed with a personal medical approach (18).

HIV in children

A) nce of HIV in children

Children, who made up about 10% of new HIV infections worldwide and comprised an estimated 3.4 million HIV-positive children under 15 in 2010 (19), have been severely impacted by the HIV pandemic. Since introducing antiretroviral treatment (ART), child survival has considerably risen in resource-rich and resource-limited settings (20). Despite an increase in ART coverage, only around 34% of children under 15 who need treatment in low- and middle-income countries get it, compared to 68% of adults (21).

B) Risk of mother-to-child transmission

Researchers found 288 out of 11,285 kids (2.6%) had HIV-related diagnoses. The majority of children (272, 94.4%) were identified as having HIV by a positive HIV fast antibody test performed after the age of 12 months or by a positive HIV-1 DNA test (22). Only 16 out of 288, or 5.6%, of the youngsters had an HIV diagnosis that was considered severe. Infected with HIV at eight weeks: 0.7% (95% CI: 0.6-0.9) of the enrolling children (23). By the time they were 12 months old, 2.2% (95% CI: 1.9-2.5) of the children had been diagnosed; by the time they were 30 months old, 2.6% (95% CI: 2.3-2.9) (22). The cumulative incidence was 0.8% (95% CI: 0.7-1.0) by age eight weeks, 2.7% (95% CI: 2.4-3.1) by age 12 months, and 5.3% (95% CI: 4.7-5.9) by age 30 months in the weighted analysis, which takes into account unobserved test findings from children lost to follow-up or not tested (22).

C) Growth and development

Even without overt AIDS or wasting, children with PHIV tend to be shorter in height, have lower body weights, and enter puberty later than children without the virus (24). Numerous conditions, including viremia, symptomatic HIV infection, malabsorption, inflammation, mitochondrial toxicity, psychosocial conditions, nutritional deficiencies, aberrant nitrogen balance, and altered growth hormone production or action, are linked to this atypical growth (25). The date of pubertal start (Tanner stage2) was considerably delayed for 2086 PHIV compared to 453 HIV-exposed uninfected children according to research employing two large US longitudinal cohorts between 2000 and 2012. The research also discovered that among PHIV, longer HAART duration was linked with somewhat more normal pubertal onset and that higher VL and lower CD4% were related to more delayed pubertal onset (26). These findings imply that early access to HAART promotes more typical development patterns for PHIV (9). However, there are few findings from the SSA where children are more likely to experience malnutrition and other disorders linked to poor growth (27).

D)Sexual and reproductive health

It has been shown in studies that having an STI increases the risk of HIV acquisition and transmission (28), but it is less clear if those with HIV who are on HAART and have a well-controlled HIV infection are more at risk for STIs (29). There is less research on PHIV, despite several studies showing the significant incidence of STIs among adolescents and young adults who are HIV-positive by behavior (30). In comparison to matched, uninfected controls, a study of 638 PHIV-positive teenage girls in the PACTG 219C cohort found higher rates of condylomas acuminate, trichomoniasis, and cervical abnormalities, such as atypical cells, low-grade, squamous intraepithelial lesions, and

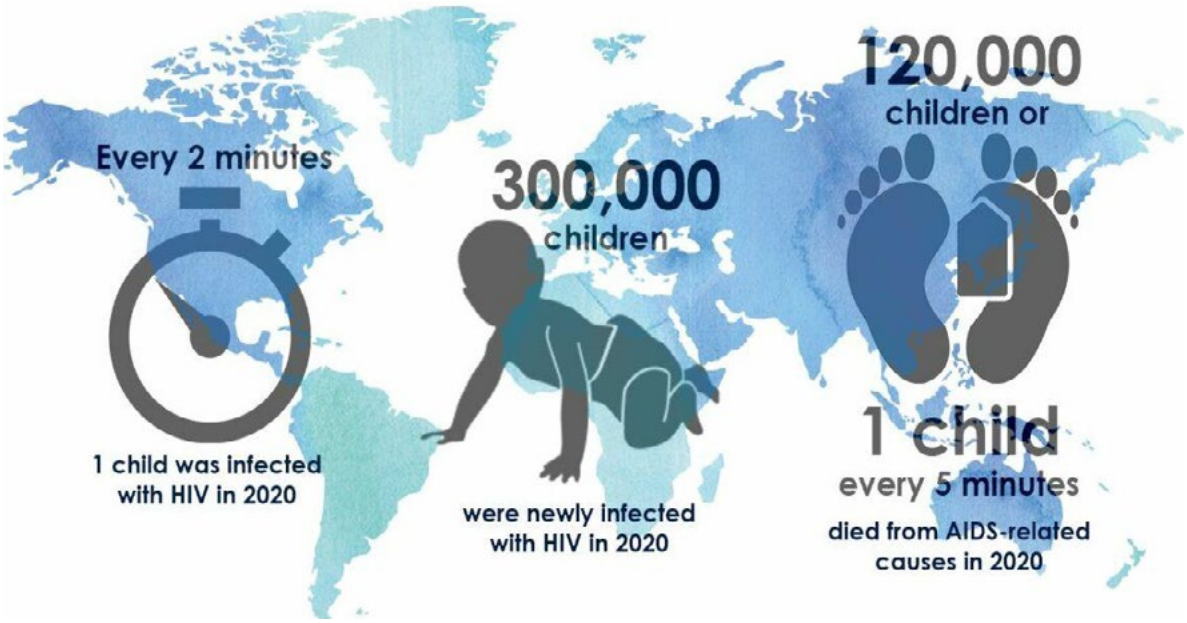

Fig 1. At least one child globally was infected with HIV every two minutes in 2020. (69)

high-grade squamous intraepithelial lesions (26). Compared to the general population, both groups of PHIV and behaviorally infected women in the United States had higher rates of pregnancy and premature births. PHIV women were significantly more likely to elect a pregnancy termination (26). In comparison to uninfected infants born to non-perinatally HIV-infected mothers, uninfected infants born to PHIV mothers were significantly shorter throughout the first year of life (after adjusting for confounding), according to a recent retrospective cohort study of 152 pregnancies in the United States (26). However, the significance of these findings is unclear. Only a small amount of data is available to guide sexual and reproductive therapies in PHIV (31). In a recent systematic analysis, it was determined that women's outcomes, such as the prevalence of HIV and STIs, the use of condoms and other contraceptives, and their retention in care, were better when sexual and reproductive health services were linked with HIV/AIDS services (32). As more people with HIV approach adolescence and adulthood, it is essential to look at more efficient service delivery systems for sexual and reproductive health care (33). Additionally, the seldom acknowledged problem of the sexual and reproductive health of PHIV-men must be addressed (26).

Antiviral inhibitors drug resistance in HIV

Human immunodeficiency virus type 1 (HIV-1) was first identified as the source of the HIV/AIDS epidemic in the early 1980s (34). Approximately 33 million people have perished from the illness in the last 40 years. The three viral enzymes, protease (PR), reverse transcriptase (RT), and integrase (IN), as well as various phases of the viral lifecycle, have all been the subject of multiple antiretroviral medication developments (35). The World Health Organization advises using these antiviral medications in combination with treatment because of their significant efficacy (35). Pre-exposure prophylaxis depends on using RT and IN inhibitors without an HIV vaccine. Treatment for HIV/AIDS relies heavily on antiviral medicines that specifically target the retroviral protease of the human immunodeficiency virus (HIV) (36). This therapy's main drawback is developing antiviral medication resistance, which affects many treated patients and builds up throughout treatment (37).

Types of drug resistance in HIV

A) Transmitted drug resistance

HIV drug-resistant strains may spread from patient to patient, causing newly infected individuals to carry drug-resistant viruses even if they have not yet started antiretroviral therapy. This is referred to as transferred medication resistance and poses a severe risk to the transmission of HIV (38, 62, 63).

B)Acquired drug resistance during antiretroviral treatment

Patients receiving antiretroviral therapy (ART) often see a gradual rise in acquired drug resistance over time (39).

C) Multi-class drug resistance

When a virus develops resistance to one medicine and then develops resistance to another drug from a different class, this phenomenon is known as multi-class drug resistance. Although it is theoretically feasible for a virus to acquire many medication-resistance mutations concurrently, the facts indicate that this is uncommon (40).

D) Resistance to the newer drugs

NRTIs, NNRTIs, and PIs were the only three main medication classes initially available for the treatment of HIV (41). However, the significant cross-resistance across these classes made it unlikely for another NNRTI to be helpful if a patient did not react to one (38). Elvitegravir and raltegravir are examples of integrase strand transfer inhibitors (INSTIs), CCR5 antagonists like maraviroc, and fusion inhibitors like enfuvirtide that were released into the market in 2003(42). There might also be wide genetic variations in drug resistance for the new medication classes. For instance, raltegravir and elvitegravir may resist single mutations, whereas newer integrase inhibitors like DTG and MK-2048 may resist numerous mutations (38). To assess how susceptible HIV is to various antiretroviral medications, resistance tests have been created. There are now two different kinds of tests: genotypic tests, which look for resistance mutations, and phenotypic tests, which gauge a virus's sensitivity to different medications in tissue-culture systems (43, 72).

Phenotypic resistance tests examine viruses' susceptibility to various medications in vitro, and the findings may be very instructive in a research context. However, because of its intricacy, expense, and time commitment (requiring more than a week to complete), this sort of assay is not appropriate for routine clinical testing. Genotypic resistance testing is an alternate strategy that entails sequencing the relevant viral genome segments and analyzing the sequence in light of the virus›s resistance phenotype (44, 64-66).

Forecasting the establishment of medication resistance requires knowing how HIV replicates during treatment (45). HIV infection that persists after treatment indicates the chance that the virus may continue to spread actively and lead to new mutations and medication resistance. On the other hand, the likelihood of new drug-resistance mutations arising from long-lived, chronically infected reservoirs is significantly lowered if treatment suppression successfully stops the infection from spreading (46).

Human immunodeficiency virus (HIV) presents

Table 1. Multi-class drug for HIV treatment.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) [61]	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) [62]	Protease inhibitor (PI) [63]	Integrase inhibitors [64]	Post-binding inhibitor or monoclonal antibody [65]	Drugs based on integrase strand transfer inhibitor (INSTI) [66]	Drugs based on nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) [67]
Abacavir	Cabotegravir	Atazanavir	Cobategravir and Rilpivirine	Atazanavir + Cobicistat	Bictegravir + Tenofovir Alafenamide + Emtricitabine	Abacavir + Lamivudine
didanosine	Delavirdine	Darunavir	Cabotegravir	Darunavir + Cobicistat	Dolutegravir + Aabacavir + lamivudine	Abacavir + Lamivudine + Zidovudine
Emtricitabine	Doravirine	Fosamprenavir	Dolutegravir	Elvitegravir + TDF + FTC + Cobicistat	Dolutegravir + Rilpivirine	Tenofovir Alafenamide + Emtricitabine
lamivudine	Efavirenz	Indinavir	Elvitegravir	Elvitegravir + TAF + FTC + Cobicistat	Dolutegravir + lamivudine	Tenofovir disoproxil Fumarate + Emtricitabine
Stavudine	Etravirine	lopinavir + ritonavir	Raltegravir	---	Elvitgravir + Cobicistat + Tenofovir Alafenamide + Emtricitabine	Tenofovir disoproxil Ffumarate + lamivudine
Tenofovir alafenamide	Nevirapine	Nelfinavir	---	---	Elvetgravir + Cobicistat + Tenofovir Disoproxil Fumarate + Emtricitabine	Zidovudine + Lamivudine
Tenofovir disoproxil fumarate	Rilpivirin	Ritonavir	---	---	---	---
Zidovudine	---	Saquniavir	---	---	---	---
	---	Tipanavir	---	---	---	---

one of the highest evolutionary rates ever detected, and a combination of antiretroviral therapy is needed to overcome the plasticity of the virus population and control viral replication (47, 71). Conventional treatments cannot clear the latent reservoir, which remains the major obstacle towards a cure. Novel strategies, such as CRISPR/Cas9 gRNA-based genome editing, can permanently disrupt the HIV genome. However, HIV genome editing may accelerate viral escape, questioning the approach's feasibility (48). Here, we demonstrate that CRISPR/Cas9 targeting single HIV loci only partially inhibits HIV replication and facilitates rapid viral escape at the target site (49). A combinatorial approach of two strong gRNAs targeting different regions of the HIV genome can completely abrogate viral replication and prevent viral escape (50). Our data shows that the accelerating effect of gene editing on viral escape can be overcome. As such, gene editing may provide a future alternative to control HIV infection (51).

Efficient targeting and editing of HIV by CRISPR/Cas9 The researchers evaluated the ability of stably expressed gRNAs to target and edit HIV DNA. Two gRNA sequences designed to target the HIV-1 LTR region were expressed in a lentiviral vector with Cas9 endonuclease (52). GRNAs were intended to target the viral structural matrix protein, protease, reverse transcriptase, and integrase, all essential for virus replication (53). The researchers infected Jurkat cells containing a nearly complete copy of HIV with gRNA-containing lentiviruses that target the LTR region, the matrix structural protein, or the integrase enzyme (54). Deep sequence analysis revealed specific genome editing events at the target site in 100%, 76%, and 90.1% of the sequences for LTR6, MA3, and IN5 gRNAs, respectively (47). Therefore, the researchers focused on the LTR region and selected two gRNAs, LTR4 and LTR6, which target the SPI binding region and the TAR loop (47, 70).

Gene Editing of HIV-1 Co-receptors to Prevent and/or Cure Virus Infection

Functional or sterilizing treatment can be achieved using gene editing technologies, which show promise both in vitro and in vivo. To be a successful treatment, gene editing efficiency needs to be increased. Successful gene editing technologies are a desirable alternative for HIV-1 therapy of the future due to their potential

advantages (55). All gene editing approaches must overcome obstacles before they can be developed into an appealing curative HIV-1 therapy. Any gene editing technique to combat HIV-1 will also face difficulties detecting and altering cells at various anatomical areas or altering precursor cells that eventually go to tissue sites. For any in vivo gene editing approach, a delivery system that can be transported to multiple locations will be highly beneficial (56). It is unclear if tissue-resident cells have been effectively changed using gene editing of HIV co-receptors in vivo. Nevertheless, the ability to engraft into various tissue compartments has been demonstrated when hematopoietic stem/progenitor cells are edited with a ZFN targeting CCR5(57). Infected NHPs' guts may be replenished with virus-repleted CD4 central memory T cells using these modified cells. The peripheral blood reservoir and all latent viral reservoirs are anticipated unaffected by co-receptor editing for HIV-1 infection. For instance, it would be less likely to target tissue-resident cells successfully (58). Absent a greater knowledge of the mechanism underlying the "Cure" of the "Berlin Patient," ablation of the CCR5 receptor in CD4 T cells has come to dominate research in this field (59). Delivering Cas9/sgRNA ribonucleoproteins directly to infected cells rather than plasmids has reduced off-target effects. In a recent study, R691A SpCas9 mutant delivery using human HSPCs revealed negligible off-target editing while maintaining excellent on-target activity (60). Human CD4 T cells in vitro CXCR4 expression was interfered with using Cas9 RNPs (61, 67, 68).

CONCLUSION

According to the current research, despite being at the center of the arena—providing the stage of concern its raison —people being treated for HIV were both involved by others and marginalized. Members of professional organizations whose specialized professional interests are prioritized in the field should not overlook patients' concerns. In addition to the particular aims of the communities engaged thus far, the overarching goal of guaranteeing patients' survival must be made more tangible and enriched by patients' perspectives: What do HIV-positive patients require today? How might currently existing support networks, such as DAH, help articulate and formulate such requirements during higher-level decision-making processes on appropriate therapies and developing new tools? Single-pill regimens can assure the continued existence of most HIV-positive persons without problems. Is it the proper path to create new and more precise HIV TOS, such as NGS-based HIV TOS, which might improve digitalization and deeper analysis of patient data? Or may other activities that prioritize patients' health(care) requirements be more beneficial to the health and well-being of HIV-positive people? We encourage participatory programs that incorporate all stakeholders and a diverse range of HIV-positive persons to address the question of which HIV TOS improvements should be prioritized.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data generated or analyzed during this study are included in this article.

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