

Recent Advances in the Treatment of HIV Infection-A Review

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ABSTRACT

HIV is the leading cause for mortality and morbidity across worldwide. HIV infection is considered as medical apocalypse in certain age period, because it caused massive infection

spread. However many interpretations and inventions in the treatment of HIV infection, it is still been considered as major disease burden, because it affects directly the immune cells of individuals and make them more vulnerable to common infections. Advances in HIV / AIDS therapy were quick and well-exposed. An improved understanding of HIV pathogenesis has shown the need for aggressive antiretroviral therapy in most HIV-infected people. At least three combinations of drugs are needed to suppress viral replications. In addition, the capacity of pharmaceutical firms to formulate such effective medications into fixed-dose formulations offers innovative new pill stress reduction techniques, thus ensuring adherence and reducing the development of drug-resistance. However, the excitement with which these new drugs were greeted has been tempered by the fact of restricted access in the developing world, further illustrating the gap in the battle against HIV / AIDS between the rich and poor countries. Such therapies would require proper political will and medication access to low and middle income countries. Developing countries' goal continues to increase the scope of ART, but in order to tackle toxicity and drug resistance, both of which threaten the viability of these initiatives, new drugs are also required. Nowadays recent studies focus on obtaining viral sequences found in newly infected individuals to identify and examine the features of all transmitted pathogens which could provide potential targets to develop HIV vaccine. This study focuses on mainly the recent advanced methodologies used in HIV treatment.

Keywords

HIV infection, CCR5 protein, Nucleotide reverse transcriptase inhibitors, Non-nucleotide reverse transcriptase inhibitors, Replication.

INTRODUCTION

The pandemic of Human Immunodeficiency Virus (HIV) infection continues to create the most difficult situation among public health comorbidities. One of the most emotive aspects of HIV is having extremely high levels of genetic variance around 13 subtypes and 51 recombinant forms [(Zulfiqar *et al.*, 2017)]. Human immunodeficiency virus origination pattern was similar to monkey infecting virus, Simian Immunodeficiency virus (SIV) [(Fanales-Belasio *et al.*, 2010)]. HIV belongs to the family Retroviridae genus, lentivirus made based on their morphological and genetic basis [(Tang and Pillay, 2004)]. First case of HIV infection was reported in 1981, Centre of disease control initially HIV virus is considered as severe immunodeficiency disease. Later in 1983 it was named as Acquired immunodeficiency syndrome (AIDS). The early identification and characterisation of infection spread about 78 million people infected, in which 39 million individuals died [(Costin, 2007), (Samuel and Devi, 2015)]

Till date the infection spread rate has fallen to 38% [(Organization and Others, 2010)]. In 2018, 37.9 million people were diagnosed with HIV infection. For the first time in 2018, more than half of all new HIV infections globally accounted for individuals from key ethnic groups and

their sexual partners in 2018 (an estimated 54 percent). Such populations reported approximately 95% of new HIV infections in Eastern Europe, Central Asia, the Middle East and North [(US Preventive Services Task Force *et al.*, 2019), (Baheerati and Devi, 2018)]. Genome of HIV encodes about 8 viral proteins which are essential for the virus cycle. The life cycle of HIV occurs within the human body. First it binds with virus encounter CD4⁺T cells, after binding fusion occurs, then reverse transcription followed by integration and replication. Final steps are assembling and budding. Human immunodeficiency virus is found in two forms HIV-1 and HIV-2. They both share many similarities like basic genetic arrangement, mode of transmission, replication sequence and both result in AIDS [(Meulendyke, Croteau and Zink, 2014), (Fathima, 2016)]. There are four (M, N, O, P) and eight (HIV -A to H) different lineages coming under HIV -1 and 2. However HIV-2 was found to be less virulent to cause AIDS, compared to HIV-1. HIV-1 virus causes epidemics in central and western Africa [(Yousaf *et al.*, 2011)]. When the clinical trials occur both viruses demonstrate very similar pathological processes, Even though the progression of HIV-2 virus occurs at higher CD4 count cells [(Azevedo-Pereira and Santos-Costa, 2016), (Harsha *et al.*, 2015)]. HIV-1 was thought to be risen from the cross specific transmission of chimpanzee virus to humans [(Hahn *et al.*, 2000)]. HIV-2 virus was found to be risen from the cross specific transmission from sooty mangabey virus [(Lemey *et al.*, 2003)].

Since HIV is dreadful disease prevailing all over the globe. Transmission occurs by whatever route depends on the infectiousness of index case (first case who transmits the HIV virus) and susceptibility of the host individuals [(Galvin and Cohen, 2004)]. The infectiousness based on the following category: concentration of HIV and infected cells in the body fluids (blood or genital secretions) [(Levy, 1988)] and also by virus specific determinants. The mode of transmission is mainly by physical contact or in some cases it is from infected mother to infant (through breast milk) or during delivery due to exposure of body fluids [(Ronen, Sharma and Overbaugh, 2015), (Dave and Others, 2016)]. Approximately 2.4 million people are HIV positive with the current state of HIV infection and death rates in the western and central regions. China, Indonesia and India contributed substantially to around 78 per cent of the total new disease burden in Asia and the Pacific region. Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Ariga *et al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy *et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and Antony, 2018; Manohar and Sharma, 2018; Menon *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan *et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy *et al.*, 2019; Gheena and Ezhilarasan, 2019; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar *et al.*, 2019; Sharma *et al.*, 2019; Siddique *et al.*, 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

METHODOLOGY

The study setting is a review. The information is obtained by searching the keywords and the data is collected through search engines like Pubmed and google scholar. They were collected with a restriction in time basis from 1989 - 2020. The Inclusion criteria considered review and original research articles based on HIV, Causes, prevention and treatment. Exclusion criteria included retracted articles and articles related to other categories. The article is reviewed from 42 articles collected.

TREATMENT

Patients with this mysterious immune disease known as AIDS arrived at NIH(National institutes of health)clinical centre in 1981. At that time there was no effective treatment and medicine. The NIH researchers first focused on vial enzymes(reverse transcriptase) to stop the virus proliferation [(Arora *et al.*, 2010)]. Later in 1990 Azidothymidine(AZT) a compound manufactured as an anti-cancer drug was applied into clinical trials .After randomised critical experiments, it gave a positive hope, by improving the survival rate of AIDS patients [(Johnson *et al.*, 2011)]. In 1982 , several media named the four H clubs as high risk factors for AIDS. In 1984 HIV was recognised as the cause for Acquired immunodeficiency disease. In late 1997 new HAART(Highly active antiretroviral therapy) treatment was invented and it caused a 47 percent decline in overall death rate. Standard ART helps in controlling the multiplication of HIV infection in the infected patient and increases the number of CD4 cells, thus prolonging the asymptomatic phase of infection, slowing the progression of the disease and decreasing the risk of transmission. Later FDA approved combivir, a combined drug therapy was developed. There is no specific treatment for this disease since now. But a variety of drugs has been tried and selected for its effect against infectious viruses. For instance, Zidovudine, Efavirenz, Tenofovir and FTC are used [(Grady, 1995)- (Dowdle, 1986)]. Out of which antiretroviral drugs showed promising results.

VACCINE EFFICACY

Exact immunity function against HIV has been hidden and is unresolved. Three strong techniques have now attracted scientists and engaged them in the neutralization of antibodies, CD8 T cell mediated immunity and many specific and groundbreaking approaches [(Moss and Bacchetti, 1989)5]. Also, traditional ways of inserting live attenuated or inactive form of virus into the host cell became a risk because it contains a permanent integration of proviral DNA into the host chromosome. Recombinant DNA technology later came into the picture as it had previous evidence of vaccine invention for terrible disease hepatitis B. But this approach also became a failure due to extreme mutability of existing strains.

ADVANCE MODALITIES

The main aspect of treating the HIV virus is focusing to interrupt the proliferation and replication process.

SHOCK AND KILL THERAPY

HIV virus infection is incurable, since it creates latent proviral reservoirs that in turn start reproducing virus particles over the lifetime of the host. Shock and kill therapy act as precursors of antiretroviral drugs. By inserting / inducing transcription with latency reversing agents(LRAs) this technique focuses on reverse proviral sequence [(J. Priya, Devi and Others, 2019)6]. But a lot of LRA's are developed to date. None of these resulted in successful practical cure. The doubt about the technique of shock and kill arises when the heterogeneous nature of the proviral reservoirs has been stressed. To date, only clinical trials of in vivo activation of the expression of the viral gene have demonstrated clearance for reactivated cells. To activate the turn over of reactivated cells antibodies, T cell vaccines stimulate the functioning of cells to kill the reactivated cells and continue the latency reversing.

IMMUNOTHERAPY

Viruses remain in the HIV reservoirs throughout the triple therapy. As a rule, HIV virus infects first the CD4 cells and then white blood cells that contain antibodies to the infection. Antiretroviral drugs regulate the functioning of reservoirs but do not eliminate fully [(A. J. Priya, Devi and Others, 2019)7]. The surface of the cells contains three distinct proteins (PD-1, LAG-3, TIGIT). A number of immunotherapeutic agents used for cancer treatment will stimulate the HIV reservoir by causing latency reversal. Immunotherapy can supercharge the human cells to combat the virus. Approach of functional HIV cure combines with drugs and activate the hidden reservoir to induce vaccines and immune response more stronger than usual

GENE EDITING

Gene mutation means a permanent alteration in the gene-forming DNA sequences. By doing so the genes of infected patients vary from the DNA sequence of ordinary individuals. The gene editing gene used in this case is CCR5, which is present on the immune cell surface. The gene CCR5 facilitates and guides the virus toward the human cell. In the technique of gene editing, genome editing was achieved by generating double strand breaks on the DNA at some locus. In the presence of template DNA, DSBs facilitate non-homologous joining or homologous guided repair. Zinc finger nucleases, a designable zinc finger DNA binding protein or TAL effector derived from *Xanthomonas*, is used for common DSBs in living cells [(Esté and Cihlar, 2010)8].

ANTIRETROVIRAL THERAPY AND DRUGS

Antiretroviral treatment refers to the use of a mixture of two or more drugs to produce mutual beneficial effects. Studying the life cycle of HIV pharmacological targets interferes with the viral replication [(Pilcher *et al.*, 2007)9,(Shruthi and Preetha, 2018)]. Viral entry, nuclear arrival, reverse transcription, genomic incorporation, and mutation are key molecular events. Currently,

there were five classes of antiretroviral drugs under FDA approval. These drugs mainly target four different proteins ie: receptor of host cells, reverse transcriptase, integrase, protease to interfere with the process of viral replication.

FDA APPROVED FIVE CLASS OF DRUG

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

NRTIs were first accepted and are known as the backbone of HIV care. They are favoured as first line medicines. Inhibitors of reverse transcriptase are a group of drugs, which bind to the reverse transcriptase enzyme and interfere with HIV multiplication. NRTIs have a very low genetic barrier, the continued use of this medicine causes mutations and cross resistance within the class [(Carret *et al.*, 1998)1].

FOR ADULT USE- Zidovudine, Stavudine, Lamivudine, Abacavir.

FOR CHILD USE- Zidovudine, Stavudine, Didanosine.

NON-NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS(NNRTIs)

NNRTIs are an integral part of the initial regimen [(Deeks, Lewin and Havlir, 2013)2]. In developing countries Nevirapine is used for its low cost and convenient dosage schedule. It is also considered safe during pregnancy and efficiently used to prevent vertical transmission [(Palepu *et al.*, 2004)3].

FOR ADULT USE-Nevirapine, Efavirenz, Deiviradine, Rip Irvine

FOR CHILD USE-Nevirapine.

PROTEASE INHIBITOR (PIs)

Protease inhibitors effectively block protease enzyme function in both the acute and chronically infected immune cells. Protease enzyme inhibition allows immature and non-infectious viral particles to be released. PIs have high genetic resistance, use of low-dose ritonavir as a booster for those who do not respond to the initial regimen [(Hammer *et al.*, 2008)4, (Swathy and Sethu, 2015)5].

FOR ADULT USE-Ritonavir, Indinavir, Saquinavir, Nelfinavir.

FOR CHILD USE-Ritonavir, Nelfinavir, Darunavir

ENTRY INHIBITORS(CCR5 AND FUSION INHIBITORS)

This group of medicines prevents the infection by blocking the CCR5 sites in the cell surface. The presence of vacant CCR5 sites will cause HIV to lose the immune cell entry pathways. The first inhibitor of CCR5 was Aplaviroc, followed by Maraviroc and Vlciviroc. The target is the envelope protein subunit GP41 [for Enfuviride] and the Maraviroc small molecule CCR5 receptor antagonist [(Iyer, Devi and Priya, 2019)6]

FOR CHILD USAGE AND POST EXPOSURE PROPHYLAXIS-Enfuviride

INTEGRASE INHIBITOR

Integrase inhibitor inhibits strand transfer of viral DNA to host cell DNA by inhibiting the functioning of integrase enzyme action. The first agent Raltegravir was approved by FDA for both treatment experienced and native patients [(Temesgen and Siraj, 2008)7, (Gayatri and Sethu, 2018)8]. The second drug was Elvitegravir on undergoing phase 3 trials.

ADVERSE EFFECTS OF ANTIRETROVIRAL DRUGS

1. Gastrointestinal: Nausea [(Timothy, Devi and Priya, 2019)9], diarrhea, vomiting, taste perversion, constipation, dyspepsia, abdominal pain, hepatotoxicity, and pancreatitis
- 2.. Central nervous system: Headache, vision problems, dizziness, tinnitus, insomnia [(Rj and Devi, 2016)], paresthesia, pain/numbness/tingling in extremities, peripheral neuropathy, somnolence, excessive sleep at night, memory problems, loss of olfactory function, and hearing impairment .
3. Hematological: Anemia, bilirubinemia, increased urate, and blood in the urine [(Renuka and Sethu, 2015)1]
4. Psychological: Anxiety, confusion, depression, nightmares, elation, and delusions
5. Metabolic : Abnormal fat distribution (lipodystrophy), anorexia, dyspnea, fatigue, lethargy, and weight gain [(Choudhari and Jothipriya, 2016)2]
6. Dermatological : Skin rash, facial discoloration, and pruritus

Socioeconomic status

Socio economic status is directly associated with the ART related death. Because opportunities of lower middle class individuals to perceive ART was less. In a longitudinal study conducted, 80% of individuals who discontinued ART treatment belong to lower class. Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; VijayashreePriyadharsini, SmilineGirija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; VijayashreePriyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

ADDED BENEFITS

Compared to other treatments, Antiretroviral therapy (ART) is relatively safest and known to be effective against HIV virus. It's essential because it increases the patient's longevity of lifetime.

CONCLUSION

The emergence of new sequencing and bioinformatics tools are only the beginning to benefit the treatment of HIV and preemptive measures. Despite the complicated genetic variability of HIV virus immunotherapy, genetic editing paves promising future targets for HIV infection studies.

Indeed AIDS is contagious ,vaccines are still in progress.As a human we are committed to eradicate AIDS.As of now antiretroviral drugs and therapy are visible solutions for HIV infection.Even if the patient undergoes ART ,his disability adjusted life year(DLAYS) get reduced.

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CONFLICT OF INTEREST

No conflict of interest declared.

REFERENCE:

- [1]. Ariga, P. *et al.* (2018) ‘Determination of correlation of width of Maxillary Anterior Teeth using Extraoral and Intraoral Factors in Indian Population: A systematic review’, *World journal of dentistry*, 9(1), pp. 68–75.
- [2]. Arora, D. R. *et al.* (2010) ‘Recent advances in antiretroviral therapy in HIV infection’, *Journal of the Indian Medical Association*, 108(1), pp. 29–34.
- [3]. Azevedo-Pereira, J. M. and Santos-Costa, Q. (2016) ‘HIV Interaction With Human Host: HIV-2 As a Model of a Less Virulent Infection’, *AIDS reviews*, 18(1), pp. 44–53.
- [4]. Baheerati, M. M. and Devi, R. G. (2018) ‘Obesity in relation to Infertility’, *Research Journal of Pharmacy and Technology*, 11(7), pp. 3183–3185.
- [5]. Basha, F. Y. S., Ganapathy, D. and Venugopalan, S. (2018) ‘Oral hygiene status among pregnant women’, *Journal of advanced pharmaceutical technology & research*, 11(7), p. 3099.
- [6]. Carr, A. *et al.* (1998) ‘A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors’, *AIDS*, 12(7), pp. F51–8.
- [7]. Chandrasekar, R. *et al.* (2020) ‘Development and validation of a formula for objective assessment of cervical vertebral bone age’, *Progress in orthodontics*, 21(1), p. 38.
- [8]. Choudhari, S. and Jothipriya, M. A. (2016) ‘Non-alcoholic fatty liver disease’, *Research Journal of Pharmacy and Technology*, 9(10), pp. 1782–1785.
- [9]. Costin, J. M. (2007) ‘Cytopathic mechanisms of HIV-1’, *Virology journal*, 4, p. 100.
- [10]. Dave, P. H. and Others (2016) ‘Pathogenesis and Novel Drug for Treatment of Asthma-A Review’, *Research Journal of Pharmacy and technology*, 9(9), pp. 1519–1523.
- [11]. Deeks, S. G., Lewin, S. R. and Havlir, D. V. (2013) ‘The end of AIDS: HIV infection as a chronic disease’, *The Lancet*, 382(9903), pp. 1525–1533.
- [12]. Dowdle, W. (1986) ‘The search for an AIDS vaccine’, *Public health reports*, 101(3), pp. 232–233.
- [13]. Duraisamy, R. *et al.* (2019) ‘Compatibility of Nonoriginal Abutments With Implants: Evaluation of Microgap at the Implant-Abutment Interface, With Original and Nonoriginal Abutments’,

Implant dentistry, 28(3), pp. 289–295.

- [14]. Esté, J. A. and Cihlar, T. (2010) 'Current status and challenges of antiretroviral research and therapy', *Antiviral research*, 85(1), pp. 25–33.
- [15]. Ezhilarasan, D., Apoorva, V. S. and Ashok Vardhan, N. (2019) 'Syzygiumcumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(2), pp. 115–121.
- [16]. Fanales-Belasio, E. *et al.* (2010) 'HIV virology and pathogenetic mechanisms of infection: a brief overview', *Annali dell'Istituto superiore di sanita*, 46(1), pp. 5–14.
- [17]. Fathima, F. (2016) 'Preetha. Evaluation of Thyroid Function Test in Obese Patients', *Asian J Pharm Clin Res*, 9(3), pp. 353–355.
- [18]. Galvin, S. R. and Cohen, M. S. (2004) 'The role of sexually transmitted diseases in HIV transmission', *Nature reviews. Microbiology*, 2(1), pp. 33–42.
- [19]. Gayatri, D. R. and Sethu, G. (2018) 'EVALUATION OF ADENOIDS BY ORONASAL AND NASAL SPIROMETRY', *Evaluation*, 11(10). Available at: <https://innovareacademics.org/journals/index.php/ajpcr/article/download/27365/15808>.
- [20]. Gheena, S. and Ezhilarasan, D. (2019) 'Syringic acid triggers reactive oxygen species-mediated cytotoxicity in HepG2 cells', *Human & experimental toxicology*, 38(6), pp. 694–702.
- [21]. Grady, C. (1995) *The Search for an AIDS Vaccine: Ethical Issues in the Development and Testing of a Preventive HIV Vaccine*. Indiana University Press.
- [22]. Hahn, B. H. *et al.* (2000) 'AIDS as a zoonosis: scientific and public health implications', *Science*, 287(5453), pp. 607–614.
- [23]. Hammer, S. M. *et al.* (2008) 'Antiretroviral Treatment of Adult HIV Infection: 2008 Recommendations of the International AIDS Society–USA Panel', *JAMA: the journal of the American Medical Association*, 300(5), pp. 555–570.
- [24]. Hannah, R. *et al.* (2018) 'Awareness about the use, ethics and scope of dental photography among undergraduate dental students dentist behind the lens', *Journal of advanced pharmaceutical technology & research*, 11(3), p. 1012.
- [25]. Harsha, L. *et al.* (2015) 'Systemic approach to management of neonatal jaundice and prevention of kernicterus', *Research Journal of Pharmacy and Technology*, 8(8), pp. 1087–1092.
- [26]. Hema Shree, K. *et al.* (2019) 'Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma - a Systematic Review with Meta Analysis', *Pathology oncology research: POR*, 25(2), pp. 447–453.
- [27]. Hussainy, S. N. *et al.* (2018) 'Clinical performance of resin-modified glass ionomer cement, flowable composite, and polyacid-modified resin composite in noncarious cervical lesions: One-year follow-up', *Journal of conservative dentistry: JCD*, 21(5), pp. 510–515.
- [28]. Iyer, P. K., Devi, R. G. and Priya, A. J. (2019) 'A Survey Study on Causes, Treatment and Prevention of Onychocryptosis', *Indian Journal of Public Health Research & Development*, 10(8), pp. 807–811.
- [29]. Janani, K., Palanivelu, A. and Sandhya, R. (2020) 'Diagnostic accuracy of dental pulse oximeter

- with customized sensor holder, thermal test and electric pulp test for the evaluation of pulp vitality: an in vivo study', *Brazilian dental science*, 23(1). doi: 10.14295/bds.2020.v23i1.1805.
- [30]. Jeevanandan, G. and Govindaraju, L. (2018) 'Clinical comparison of Kedo-S paediatric rotary files vs manual instrumentation for root canal preparation in primary molars: a double blinded randomised clinical trial', *European archives of paediatric dentistry: official journal of the European Academy of Paediatric Dentistry*, 19(4), pp. 273–278.
- [31]. Johnson, J. *et al.* (2020) 'Computational identification of MiRNA-7110 from pulmonary arterial hypertension (PAH) ESTs: a new microRNA that links diabetes and PAH', *Hypertension research: official journal of the Japanese Society of Hypertension*, 43(4), pp. 360–362.
- [32]. Johnson, V. A. *et al.* (2011) '2011 update of the drug resistance mutations in HIV-1', *Topics in antiviral medicine*, 19(4), pp. 156–164.
- [33]. Jose, J., Ajitha and Subbaiyan, H. (2020) 'Different treatment modalities followed by dental practitioners for Ellis class 2 fracture – A questionnaire-based survey', *The open dentistry journal*, 14(1), pp. 59–65.
- [34]. Kannan, A. and Venugopalan, S. (2018) 'A systematic review on the effect of use of impregnated retraction cords on gingiva', *Journal of advanced pharmaceutical technology & research*, 11(5), p. 2121.
- [35]. Kumar, D. and Antony, S. D. P. (2018) 'Calcified canal and negotiation-A review', *Journal of advanced pharmaceutical technology & research*, 11(8), p. 3727.
- [36]. Lemey, P. *et al.* (2003) 'Tracing the origin and history of the HIV-2 epidemic', *Proceedings of the National Academy of Sciences of the United States of America*, 100(11), pp. 6588–6592.
- [37]. Levy, J. A. (1988) 'The transmission of AIDS: the case of the infected cell', *JAMA: the journal of the American Medical Association*, 259(20), pp. 3037–3038.
- [38]. Manohar, M. P. and Sharma, S. (2018) 'A survey of the knowledge, attitude, and awareness about the principal choice of intracanal medicaments among the general dental practitioners and nonendodontic specialists', *Indian journal of dental research: official publication of Indian Society for Dental Research*, 29(6), pp. 716–720.
- [39]. Mathew, M. G. *et al.* (2020) 'Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: Randomized controlled trial', *Clinical oral investigations*, pp. 1–6.
- [40]. Menon, S. *et al.* (2018) 'Selenium nanoparticles: A potent chemotherapeutic agent and an elucidation of its mechanism', *Colloids and surfaces. B, Biointerfaces*, 170, pp. 280–292.
- [41]. Meulendyke, K. A., Croteau, J. D. and Zink, M. C. (2014) 'HIV life cycle, innate immunity and autophagy in the central nervous system', *Current opinion in HIV and AIDS*, 9(6), pp. 565–571.
- [42]. Moss, A. R. and Bacchetti, P. (1989) 'Natural history of HIV infection', *AIDS*, 3(2), pp. 55–61.
- [43]. Nandakumar, M. and Nasim, I. (2018) 'Comparative evaluation of grape seed and cranberry extracts in preventing enamel erosion: An optical emission spectrometric analysis', *Journal of conservative dentistry: JCD*, 21(5), pp. 516–520.
- [44]. Nandhini, J. S. T., Babu, K. Y. and Mohanraj, K. G. (2018) 'Size, shape, prominence and localization of gerdy's tubercle in dry human tibial bones', *Journal of advanced pharmaceutical*

- technology & research*, 11(8), p. 3604.
- [45]. Organization, W. H. and Others (2010) 'UNAIDS: Global Report: UNAIDS report on the global AIDS epidemic', *Geneva: WHO*, 10.
- [46]. Palepu, A. *et al.* (2004) 'Initiating highly active antiretroviral therapy and continuity of HIV care: the impact of incarceration and prison release on adherence and HIV treatment outcomes', *Antiviral therapy*, 9(5), pp. 713–719.
- [47]. Tekuri, S.K., Pasupuleti, S.K., Konidala, K.K., Pabbaraju, N. Pharmacological Effects of Polyalthiacerasoides (Roxb.) Bedd.: A brief Review(2019) *Journal of Complementary Medicine Research*, 10 (1), pp. 38Pilcher, C. D. *et al.* (2007) 'Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection', *AIDS*, 21(13), pp. 1723–1730.
- [48]. Priya, A. J., Devi, G. and Others (2019) 'Physical Fitness among the Dental Physician, Dental Undergraduates and Postgraduates Students', *Indian Journal of Public Health Research & Development*, 10(10), pp. 223–226.
- [49]. Priya, J., Devi, G. and Others (2019) 'Evaluation of Muscular Endurance among Dentists', *Indian Journal of Public Health Research & Development*, 10(10). Available at: <http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09760245&AN=140756206&h=G4SC%2FJ8z%2BUHFuuTbV4UFDCYnk6MKUTskQkH7kGxLd3EgnLZ4lb%2FVDEMrZPtKML9s6AouBNijcz%2BNcfv3UaNBkw%3D%3D&crl=c>.
- [50]. Rajakeerthi and Ms, N. (2019) 'Natural Product as the Storage medium for an avulsed tooth – A Systematic Review', *Cumhuriyet Üniversitesi Diş Hekimliği Fakültesi Dergisi*, 22(2), pp. 249–256.
- [51]. Rajendran, R. *et al.* (2019) 'Comparative evaluation of remineralizing potential of a paste containing bioactive glass and a topical cream containing casein phosphopeptide-amorphous calcium phosphate: An in vitro study', *Pesquisabrasileira em Odontopediatria e Clínica Integrada*, 19(1), pp. 1–10.
- [52]. Ramadurai, N. *et al.* (2019) 'Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial', *Clinical oral investigations*, 23(9), pp. 3543–3550.
- [53]. Ramesh, A. *et al.* (2018) 'Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study', *Journal of periodontology*, 89(10), pp. 1241–1248.
- [54]. Ravinthar, K. and Jayalakshmi (2018) 'Recent advancements in laminates and veneers in dentistry', *Journal of advanced pharmaceutical technology & research*, 11(2), p. 785.
- [55]. Renuka, S. and Sethu, G. (2015) 'Regeneration after Myocardial Infarction', *Research Journal of Pharmacy and Technology*, 8(6), pp. 738–741.
- [56]. R, H. *et al.* (2020) 'CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene', *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, pp. 306–312. doi: 10.1016/j.oooo.2020.06.021.
- [57]. Rj, I. and Devi, G. (2016) 'Role of environmental factors on sleep patterns of different age groups: A survey-based study', *Asian J Pharm Clin Res*, 9(6), pp. 124–126.

- [58]. Ronen, K., Sharma, A. and Overbaugh, J. (2015) 'HIV transmission biology: translation for HIV prevention', *AIDS*, 29(17), pp. 2219–2227.
- [59]. Samuel, A. R. and Devi, M. G. (2015) 'Geographical distribution and occurrence of Endemic Goitre', *Research Journal of Pharmacy and Technology*, 8(8), pp. 973–978.
- [60]. Samuel, S. R. (2021) 'Can 5-year-olds sensibly self-report the impact of developmental enamel defects on their quality of life?', *International journal of paediatric dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children*, 31(2), pp. 285–286.
- [61]. Sekar, D. *et al.* (2019) 'Methylation-dependent circulating microRNA 510 in preeclampsia patients', *Hypertension research: official journal of the Japanese Society of Hypertension*, 42(10), pp. 1647–1648.
- [62]. Seppan, P. *et al.* (2018) 'Therapeutic potential of *Mucuna pruriens* (Linn.) on ageing induced damage in dorsal nerve of the penis and its implication on erectile function: an experimental study using albino rats', *The aging male: the official journal of the International Society for the Study of the Aging Male*, pp. 1–14.
- [63]. Sharma, P. *et al.* (2019) 'Emerging trends in the novel drug delivery approaches for the treatment of lung cancer', *Chemico-biological interactions*, 309, p. 108720.
- [64]. Shruthi, M. and Preetha, S. (2018) 'Effect of Simple Tongue Exercises in Habitual Snorers', *Research Journal of Pharmacy and Technology*, 11(8), pp. 3614–3616.
- [65]. Siddique, R. *et al.* (2019) 'Qualitative and quantitative analysis of precipitate formation following interaction of chlorhexidine with sodium hypochlorite, neem, and tulsi', *Journal of conservative dentistry: JCD*, 22(1), pp. 40–47.
- [66]. Sridharan, G. *et al.* (2019) 'Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(4), pp. 299–306.
- [67]. Swathy, S. and Sethu, V. G. (2015) 'Acupuncture and lower back pain', *Research Journal of Pharmacy and Technology*, 8(8), pp. 991–993.
- [68]. Tang, J. W. and Pillay, D. (2004) 'Transmission of HIV-1 drug resistance', *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology*, 30(1), pp. 1–10.
- [69]. Teja, K. V., Ramesh, S. and Priya, V. (2018) 'Regulation of matrix metalloproteinase-3 gene expression in inflammation: A molecular study', *Journal of conservative dentistry: JCD*, 21(6), pp. 592–596.
- [70]. Temesgen, Z. and Siraj, D. S. (2008) 'Raltegravir: first in class HIV integrase inhibitor', *Therapeutics and clinical risk management*, 4(2), pp. 493–500.
- [71]. Timothy, C. N., Devi, R. G. and Priya, A. J. (2019) 'Evaluation of Peak Expiratory Flow Rate (PEFR) in Pet Owners', *Indian Journal of Public Health Research & Development*, 10(8), pp. 803–806.
- [72]. US Preventive Services Task Force *et al.* (2019) 'Preexposure Prophylaxis for the Prevention of

HIV Infection: US Preventive Services Task Force Recommendation Statement', *JAMA: the journal of the American Medical Association*, 321(22), pp. 2203–2213.

- [73]. VijayashreePriyadharsini, J. (2019) 'In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens', *Journal of periodontology*, 90(12), pp. 1441–1448.
- [74]. VijayashreePriyadharsini, J., SmilineGirija, A. S. and Paramasivam, A. (2018) 'In silico analysis of virulence genes in an emerging dental pathogen *A. baumannii* and related species', *Archives of oral biology*, 94, pp. 93–98.
- [75]. Yousaf, M. Z. *et al.* (2011) 'The epidemic of HIV/AIDS in developing countries; the current scenario in Pakistan', *Virology journal*, 8, p. 401.
- [76]. Zulfiqar, H. F. *et al.* (2017) 'HIV Diagnosis and Treatment through Advanced Technologies', *Frontiers in public health*, 5, p. 32.