# Are HAARTs beneficial for spermatozoa of HIV patients?

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**Abstract**

**Introduction:** Globally, HIV/AIDS has been ranked as the 5th largest cause of death in Southern Sub-Saharan Africa and the major cause of death in the world. The review aims to focus on the effects of highly active antiretroviral therapy (HAART) on the male gametes of HIV positive persons in order to give an insight into the fate of men infected with HIV with respect to their chances of having offsprings following the commencement of HAART.

**Methods:** This review considered all original and review articles published on Pubmed from year 2000 to 2015. A few selected, exceptionally relevant publications outside this period were also reviewed.

**Results:** HAART has been shown to improve the health, quality of life and reduction in the morbidity and mortality attributable to HIV-induced immune deficiency. It is anticipated that the survival of patients influence their fertility parameters while on treatment, with focus on young males, within the reproductive age.

**Conclusion:** A better understanding of the influence of HAART on spermatozoa in patients with HIV/AIDS undergoing therapeutic management is therefore vital for knowledge and a proactive measure in order not to add to their burden if there is expression of the desire to conceive a child.

**Keywords:** HIV/AIDS, HAART, sperm, Assisted reproductive technology, Africa

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# Sont-COEURS bénéfique pour spermatozoïdes des patients atteints du VIH?

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**Résumé**
**Objectif:** À l'échelle mondiale, le VIH / SIDA a été classée comme la 5ème plus grande cause de décès en Afrique australe sub-saharienne et la principale cause de décès dans le monde. L'examen vise à mettre l'accent sur les effets de la thérapie antirétrovirale hautement active (HAART) sur les gamètes mâles des personnes séropositives afin de donner un aperçu sur le sort des hommes infectés par le VIH par rapport à leurs chances d'avoir des descendants après le début de HAART.

**Méthodes:** Cet avis considérés tous les articles originaux et d'examen publiés sur Pubmed de l'année 2000 à 2015. Un Peu sélectionné, publications exceptionnellement pertinents en dehors de cette période ont également été examinés.

**Résultats:** HAART a été montré pour améliorer la santé, la qualité de vie et la réduction de la morbidité et de la mortalité attribuable à un déficit immunitaire induite par le VIH. Il est prévu que la survie des patients influencent les paramètres de fertilité pendant le traitement, en mettant l'accent sur les jeunes hommes, dans l'âge de procréer.

**Conclusion:** Par conséquent, une meilleure compréhension de l'influence de la multithérapie sur les spermatozoïdes chez les patients atteints du VIH / SIDA en cours de prise en charge thérapeutique est essentiel pour la connaissance et une mesure proactive afin de ne pas ajouter à leur fardeau s'il est l'expression de la volonté de concevoir un enfant .

**Mots-clés:** VIH / SIDA, la multithérapie, sperme, la technologie de reproduction assistée, Afrique

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## INTRODUCTION

Highly active antiretroviral therapy (HAART) is considered the most effective treatment for individuals with Human Immunodeficiency Virus (HIV) infection. This therapy is a combination of two or more antiretroviral drugs, usually reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs). This drug combination has been associated with reduction in the morbidity and mortality attributable to HIV-induced immune deficiency (1). With the advent of HAART, there has been a dramatic improvement in the overall prognosis with appreciable impact on the management of HIV infection, reduction in viral replication and many people infected by the virus now live with this manageable chronic condition (2,3). HAART has also demonstrated remarkable success in reducing the overall health care costs for HIV-positive individuals (4,5). Through the use of HAART, hope of parenthood has also been given to HIV patients since the therapy reduces the risk of virus transmission through specific sperm preparation techniques (6).

Despite the numerous beneficial effects of HAART, studies have shown that a number of side effects, adverse clinical events and toxicities are associated with it. A few of these clinical adverse effects associated with HAART include AIDS-related insulin resistance, hyperglycaemia, gastrointestinal and lipodystrophy symptoms (7,8), while the most common toxicity of NRTIs and NNRTIs is hepatotoxicity, which is usually due to damage of mitochondria (9,10).

There are reports that HIV is mostly common among persons of the reproductive age group. The desire to raise children exist in about one-third of these persons, thus, reproductive interest have emerged as clinically important in patients with HIV infection (11). It is worth noting that the pandemic of HIV, which causes Acquired Immune Deficiency Syndrome (AIDS), is one of the most important public health issues threatening the survival of several millions of people in Sub-Saharan Africa. The pandemic of the virus has threatened the development and economy of many countries in this region (12). The information available on the effect of anti-HIV-1 drug usage on male reproductive function is limited, therefore, this review article is aimed at presenting an update on existing reports that are available on the adverse effect of anti-HIV-1 combination for treating HIV-1-infected and/or AIDS patients on the male gamete. It is envisaged that this information will be highly useful for academic, research and therapeutic purposes.

## MATERIALS AND METHODS

This review considered all original and review articles published on Pubmed from 2000 to 2015. Few selected, exceptionally relevant publications outside this period were also reviewed. Only relevant studies published in English were considered and key words such as; 'HIV/AIDS, HAART, Sperm, Assisted reproductive technology, Africa' were used for the search.

## RESULTS

### History and Pandemic of HIV

HIV is established as the causative agent of AIDS. This disease of humans is caused by two lentiviruses; human immunodeficiency viruses types 1 and 2 (HIV-1 and HIV-2). AIDS is an infectious disease which was first recognized in 1981 (13,14) and ever since then, it has become one of the most challenging diseases to be discovered in recent history (15). The origin of the HIV-1 and HIV-2 has been associated with zoonotic transfer of the viruses from primates to man in Africa. HIV-1 has long been suspected to be of chimpanzee origin (16), while a sooty mangabey (type of old world monkey) origin of HIV-2 was first proposed in 1989 (17). HIV-1 comprises of four distinct lineages, termed groups M, O, N, and P, each of these groups is as a result of independent cross-species activities. The first group to be discovered was M; it represents the pandemic form of HIV-1 infecting severally millions of people in the worldwide and is found in almost all countries (18). In 1990, Group O was discovered. This group has a lower prevalence than M and represent less than 1% of global HIV-1 infections and is mainly restricted to a few African countries (19). Group N, with an even lesser prevalence than O, was identified in 1998 (20). Thus far only 13 cases have been documented, all of which in Cameroon (21), while Group P was discovered in France in 2009 in a Cameroonian woman (22) and subsequently in one other person also from Cameroon. HIV-2 is largely restricted to West Africa, with Senegal and Guinea-Bissau having the highest prevalence rates recorded (22). However, HIV-1 is increasingly replacing HIV-2, thus, there is a decline in overall prevalence of HIV-2 (23)

Interestingly, most people infected with

HIV-2 do not have AIDS but have clinical symptoms indistinguishable from HIV-1 (24). Since the first isolation of HIV-2, at least eight distinct lineages have been identified, with each representing an independent host transfer. These are groups A–H. Both groups A and B have been found to spread within humans. Group A has been isolated in West Africa, (25) and group B in Ivory Coast (26). Groups C, G, and H have also been associated with Ivory Coast, group D with Liberia and groups E and F with Sierra Leone (27,28,29).

The spread of HIV-1 is primarily through sexually transmitted disease (30), however, perinatal and percutaneous routes have also been implicated in the spread (30). The HIV-1 pandemic has claimed more than 25 million lives out of the over 60 million people infected with the virus. The greatest morbidity and mortality of HIV/AIDS has been experienced by developing countries in Sub-Sahara Africa, with the young adult population being the most vulnerable. From an epidemiologic point of view, HIV pandemic in Southern Africa has increased annually by a prevalence rate higher than 10%, thus making it the region hardest hit in the world. Surveys across the Southern African region indicates that Zambia recorded an HIV prevalence of 15.6% in the Zambia Demographic and Health Survey between 2000–2001 (31), Namibia (individuals ages 15–49 years) was 10% in 2005 (32) 4.5% in the Democratic Republic of Congo is infected (33) and 14.4% in the Malawi Demographic and Health Survey in 2004 (34). HIV/AIDS was ranked the 5th largest cause of death in Southern Sub-Saharan Africa in 1990, whereas in 2010, it was the leading cause of death (35). Braveman *et al.,* (36) reported that in the United States, 850 000 to 950 000 persons are estimated to be living with HIV, with increased incidence rate each year and since a large population of the working class are affected, issues of employment, work rehabilitation, and AIDS are major cause of concern in the work place.

**Antiretroviral Therapy versus Highly Active Antiretroviral Therapy**

The combined use of more than one antiretroviral drug (ARV) which acts on different viral targets is referred to as HAART. ARVs are used primarily to treat HIV, but broadly speaking they are used for the treatment of infection by retroviruses. This drugs act at different progression stages of HIV infection and belong to different classes. The effective treatment of HIV started with nucleoside analogue reverse transcriptase inhibitors (NRTI). Zidovudine, belonging to this class, was the first to be approved by the Food and Drug Administration (FDA) in 1987 as shown in table 1. Presently, HAART available for therapeutic use consists of drugs from five classes, NRTIs, NNRTI, PIs, Fusion or entry inhibitors and integrase inhibitors (INSTI). The latter two were recently added (37). Conventionally, ARVs are not capable of complete eradication of HIV from the body, and reports on clinical trials indicate that current vaccine strategies are not completely effective. However, overall prognosis has improved dramatically with the advent of ART associated with reduced mortality and morbidity rates (38). Usually patients are advised to take medication for longer durations so as to increase the blood count of CD4 and T-lymphocyte cells and reduce the viral load. Prolonged intake of these drugs can result in a number of metabolic disorders in these patients (39) as the different antiretroviral drugs have been reported to induce varying forms of toxicity, such as hepatotoxicity, pancreatitis, hyperlipidemia, renal failure, peripheral neuropathy, myopathy and gastrointestinal disorders (40,41). It is also well known that HIV-1 selects some drug-resistant mutants due to anti-HIV-1 drug pressure (42,43), while there is further aggravation of illness due to discontinuation of the ART treatment as a result of the side effects of anti-HIV-1 chemotherapeutics. The limitations associated with ART prompted investigation into a new, safer HIV-1 therapeutic approach that will be more cost effective with little or no toxic effects in patients.

Therapy which comprise of at least two classes of drugs was seen as a better approach and has since become the standard of care for HIV-1 infection or AIDS disease.

It is possible to combine three classes of HIV-1 inhibitors, i.e. NRTIs, NNRTIs, and PIs. NRTIS will remain an important part of HAART for some time because of its ability to enhance the virucidal potency of the regimens. HAART decreases the patient's total burden of HIV, maintains function of the immune system, and prevents opportunistic infections that often lead to death (44).

The introduction of the term HAART was in 1996 after clinical trials illustrated the beneficial effects of combining two NRTIs with PIs (44). Since these findings, HAART was used in

clinical practice and thereafter, there has been a 60% to 80% decline in the rate of hospitalization and death associated with AIDS (45). HAART defends against resistance by preventing the replication of HIV and reduces the chances of a superior mutation (46) which no individual antiretroviral drug has been able to demonstrate. HAART is usually a combination of three drugs from at least two different classes. Drug companies now combine 3 drugs into one tablet. This is to be taken only once daily, thereby making it easier for patients to take, resulting in better adherence and compliance (47). The most recent HAART regimens approved as of May 2014 consist of three drugs: 2 NRTIs with a PI or NNRTI or INSTI.

**HIV and Spermatozoa**

CD4, a glycoprotein on the surface of immune cells, is the main receptor of HIV and HIV-1 uses this to gain access into the host cells. These CD4 co-receptors are absent in spermatozoa, thus, the mechanism of spermatozoa and HIV is still debatable (48). However, other receptors of HIV present on the spermatozoa have been described. GalAAG, a glycolipid present on the spermatozoa is an alternative receptor used by HIV, but studies have shown that binding is inhibited by seminal plasma (49). CCR5 is also a co-receptor present on spermatozoa and may allow the binding of HIV to the spermatozoon if present (50). Fanibunda *et al.* (51) suggested that the mannose receptor, which was present in 10% of the ejaculates, could allow the binding of HIV gp120 to spermatozoa. However, no internalization of gp120 was observed in the study and there is no information on the possibility of the receptor triggering the internalization of the virion. The general assumption is that a motile sperm is not infected. Baccetti *et al.* (52) reported that polymerase chain reaction (PCR) detected DNA and /or RNA of HIV in purified spermatozoa, retrieved via a gradient of Percoll without swim-up, however several authors have concluded that the presence of infection might be a false positive or contaminations by infected leucocytes (53,54,55,56). The presence of HIV DNA has been associated with abnormal sperm morphology in a subset of ejaculates using a range of techniques (57). It has been hypothesised that the possibility of a non-specific uptake of DNA and/or RNA of HIV by epididymal spermatozoa would lead to sperm abnormality which may explain the detection of the DNA of HIV associated with abnormalities or the detection is a function of specific interaction between the spermatozoa and HIV (58). It can therefore be concluded that the mechanism of interaction between HIV and spermatozoa and its effect on sperm characteristics is still poorly understood and requires further investigation. However, some studies have investigated the spermatozoa characteristics of HIV patients before the commencement of HAART and their findings show no correlation between sperm fertilizing parameters and duration of HIV infection in these patients (59,60). Investigation into the effect of HIV dates back as early as the 1990s, the effect of HIV on sperm characteristics was investigated. Interestingly, there was no significant difference in the sperm parameters of HIV positive patients when compare to healthy seronegative semen donors (53).

**Interplay between HIV, HAART and Sperm**

It is important to note that the majority of HIV infected persons are on HAART, thus these drugs may affect sperm functionality, independently or in addition to the infection. Various studies on the association of HIV, HAART and spermatozoa are available in the literature, but there are a lot of discrepancies in these reports. (53,61,62 ). These differences in published findings might be as a result of methodological dissimilarity, differences in progression of disease in patients and treatment regimens as well as the wide variation in the choice of controls used for the studies. Nevertheless, patients on HAART in the early stage of HIV infection had semen parameters comparable with the control group while with progression of disease, a detrimental effect was observed on sperm qualities (53,63 ,64). In most of the studies, one of the sperm parameters (motility, concentration, morphology, volume and viability) significantly correlated with number of CD4+ blood cells. (63,61,62). Several studies have evaluated the sperm parameters of HIV patients on HAART and have reported different findings. However, most of these studies found alterations in semen parameters. Sperm motility and morphology was significantly reduced in HIV patients on HAART (64-67) while there were no significant changes in these sperm parameters in other studies (53,63). Some studies reported no alteration in sperm morphology (63,68) while a decrease in ejaculated volume has also been associated with HIV patients on therapy (53,64,65). No

significant change was observed in sperm morphology and ejaculated volume in several other studies (61-63,66,67). Spermatozoa concentrated was not also altered (53,61,63,68 ) while a significant reduction in concentration was noticed in few studies (62,64).

The reduction in sperm motility is associated with mitochondrial toxicity which is associated with nucleoside analogs; an important component of HAART (69,70). Pavili et al. (67) also linked reduced sperm concentration, motility and normal morphology with the decrease in spermatozoon mitochondrial DNA content in semen of HIV-infected patients treated with HAART.

In a recent study, it was observed that men infected with HIV who are on HAART showed significant decreases in sperm motility, vitality, normal morphology and semen volume. Interestingly an improvement sperm-oocyte penetration rate was observed when compared to healthy controls (60). This is in variance to a prior report that observed no significant effect of HAART on sperm concentration and volume, but found improvement in sperm viability and morphology during a 12-week period after the start of HAART (71). Similarly, in a study involving 34 HIV patients over 48 weeks of HAART, all sperm parameters remained unchanged, except for a decrease in progressive motility. However, it was still unclear as to whether the reduced motility will affect the possibility of fathering a child or an increased need for assisted reproductive techniques (59). Lambert-Niclot *et al.* (72) also concluded that Nevirapine, a NNRTIs was associated with improved semen quality when compared with Efavirenz while NRTIs and PIs were not associated with any semen change.

This is an indication that it is possible that HAART might improve sperm function by improving the health through better immunity status of HIV male patients since the best parameter for predicting the negative impacts of HIV on sperm quality is CD4+ blood cell count.

## CONCLUSION

It is important to note that the ARVs might affect the semen quality of patients independently or in addition to the infection. However, it is possible that the result observed is a function of the patient's health condition as a whole and not direct the effect of HIV on the spermatozoa. Hence, there is a need for further studies on the effects of HAART on sperm function and other reproductive functional parameters in the absence of HIV infection in order to conclude if HAART might be contributing adversely to sperm function of HIV/AIDS patients. More importantly, the extent to which sperm motility translates into reduced fertility needs to be further investigated.

**Conflict of interest:** None declared

## REFERENCES

1. Palella Jr. FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient Study Investigators. N. Engl. J. Med. 1998; 338, 853–860.
2. Kayode AAA, Kayode OT, Aroyeun OA, Stephen MC. Hematological and hepatic enzyme alterations associated with acute administration of antiretroviral drugs. J Pharmacol Toxicol. 2011;6 (3): 293–302.
3. Kushnir VA, Lewis W. Human immunodeficiency virus/acquired immunodeficiency syndrome and infertility: emerging problems in the era of highly active antiretrovirals. Fertil Steril. 2011; 96 (3): 546–550
4. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003; 362:22–29.
5. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre, early, and late HAART (highly active antiretroviral therapy) eras. J Acquir Immune Defic Syndr. 2006; 41:194–200.
6. Bujan L, Sergerie M, Moinard N, Martinet S, Porte L, Massip P, et al. Decreased semen volume and spermatozoa motility in HIV-1-infected patients under antiretroviral treatment. J. Androl. 2007; 28, 444–452.
7. Hagmann M. Study confirms effectiveness of antiretroviral drugs for HIV patients. Bull World Health Organ. 2003; 81(12):918–919.
8. Montessori V, Press N, Harris M, Akagi L, Montaner JS. Adverse effects of antiretrocviral

therapy for HIV infection. Can Med Assoc J. 2004;170:229–238.
9. Abrescia N, D'Abbraccio M, Figoni M, Busto A, Maddaloni A, De Marco M. Hepatotoxicity of antiretroviral drugs. Curr Pharm Des. 2005;11:3697–3710
10. Soriano V, Puoti M, Garcia-Garsco P, Rockstroh JK, Benhamou Y, Barreiro P, et al. Antiretroviral drugs and liver injury. AIDS. 2008; 22: 1–13.
11. Keiser P, Nassar N, Kvanli MB. Long-term impact of highly active antiretroviral therapy on HIV related health care costs. *J Acquir Immune Defic Syndr*. 2001;27:14–19.
12. Suave N, Dzokoto A, Opare B, Kaitoo EE, Khonde N, Mondor M, et al. The price of development: HIV infection in a semiurban community of Ghana. J Acquir Immune Defic Syndr. 2002;29:402–408
13. CDC. 1981. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. MMWR Morb Mortal Wkly Rep 30: 305–308.
14. Greene WC. 2007. A history of AIDS: Looking back to see ahead. Eur J Immunol 37 (Suppl. 1): S94–S102
15. Popovic M, Sarngadharan MG, Read E, Gallo RC. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science. 1984; 224: 497–500.
16. Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, et al. Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. Nature. 1999; 397: 436–441.
17. Hirsch VM, Olmsted RA, Murphey-Corb M, Purcell RH, Johnson PR. An African primate lentivirus (SIVsm) closely related to HIV-2. Nature. 1989; 339: 389–392.
18. Gurtler LG, Hauser PH, Eberle J, von Brunn A, Knapp S, Zekeng L, et al. A new subtype of human immunodeficiency virus type 1 (MVP-5180) from Cameroon. J Virol. 1994; 68: 1581–1585.
19. Peeters M, Gueye A, Mboup S, Bibollet-Ruche F, Ekaza E, Mulanga C, et al. Geographical distribution of HIV-1 group O viruses in Africa. AIDS. 1997; 11: 493–498.
20. Simon F, Mauclere P, Roques P, Loussert-Ajaka I, Muller- Trutwin MC, Saragosti S, et al. Identification of a new human immunodeficiency virus type 1 distinct from group M and group O. Nat Med. 1998; 4: 1032–1037.
21. Vallari A, Holzmayer V, Harris B, Yamaguchi J, Ngansop C, Makamche F, et al. Confirmation of putative HIV-1 group P in Cameroon. J Virol, 2011; 85: 1403–1407.
22. de Silva TI, Cotten M, Rowland-Jones SL. HIV-2: The forgotten AIDS virus. Trends Microbiol. 2008; 16: 588–595.
23. Hamel DJ, Sankale JL, Eisen G, Meloni ST, Mullins C, Gueye-Ndiaye A, et al. Twenty years of prospective molecular epidemiology in Senegal: Changes in HIV diversity. AIDS Res Hum Retroviruses. 2007; 23: 1189–1196.
24. Rowland-Jones SL, Whittle HC. Out of Africa: What can we learn from HIV-2 about protective immunity to HIV-1? Nat Immunol. 2007; 8: 329–331.
25. Damond F, Descamps D, Farfara I, Telles JN, Puyeo S, Campa P, et al. Quantification of proviral load of human immunodeficiency virus type 2 subtypes A and B using realtime PCR. J Clin Microbiol. 2001; 39: 4264–4268.
26. Ishikawa K, JanssensW, Banor JS, Shinno T, Piedade J, Sata T, et al. Genetic analysis of HIV type 2 from Ghana and Guinea-Bissau, West Africa. AIDS Res Hum Retroviruses. 2001; 17: 1661–1663.
27. Gao F, Yue L, White AT, Pappas PG, Barchue J, Hanson AP, et al. Human infection by genetically diverse SIVsm-related HIV-2 in west Africa. Nature. 1992; 358: 495–499.
28. Chen Z, Luckay A, Sodora DL, Telfer P, Reed P, Gettie A, et al. Human immunodeficiency virus type 2 (HIV-2) seroprevalence and characterization of a distinct HIV-2 genetic subtype from the natural range of simian immunodeficiency virus-infected sooty mangabeys. J Virol. 1997; 71: 3953–3960.
29. Santiago ML, Range F, Keele BF, Li Y, Bailes E, Bibollet- Ruche F, et al. Simian immunodeficiency virus infection in free-ranging sooty mangabeys (Cercocebus atys atys) from the Tai Forest, Cote d'Ivoire: Implications for the origin of epidemic human immunodeficiency virus type 2. J Virol. 2005; 79: 12515–12527.

30. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute-HIV-1 Infection: Basic, clinical and public health perspectives. N Engl J Med. 2011; 364: 1943–1954.
31. Zambia Central Board of Health. Zambia Demographic and Health Survey 2000–2001. Calverton, MD: Central Board of Health, Zambia and ORC; 2003.
32. Namibia Ministry of Health and Social Services. Follow-up to the Declaration of Commitment on HIV/AIDS (UNGASS). Namibia Country Report, 2005. Windhoek, Namibia: Namibia Ministry of Health and Social Services; 2006.
33. Democratic Republic of Congo: National Multi-Sectoral Programme for the Response to HIV/AIDS. Report of the Implementation of the Declaration of Commitment of the Heads of State and of Government for the Response to HIV/AIDS in the Democratic Republic of Congo, 2005. Kinshasa, Democratic Republic of Congo; 2006.
34. Malawi National Statistical Office, ORC Macro. Malawi Demographic and Health Survey. Calverton, MD: National Statistical Office, Zomba, Malawi and ORC Macro; 2004.
35. Lozano R, Naghavi, Foreman. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095–128.
36. Braveman B, Levin M, Kielhofner G, Finlayson M. HIV/AIDS and return to work: a literature review one-decade post-introduction of combination therapy (HAART). Work J Prev Assess Rehabil. 2006; 27(3):295–303.
37. Esté, JA and Cihlar T. Current status and challenges of antiretroviral research and therapy. Antiviral Research 85. 2010: 25–33
38. Detels R, Tarwater P, Phair JP. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. *AIDS*. 2001;15:347–355.
39. Stenzel MS, Carpenter CC. The management of the clinical complications of antiretroviral therapy. *Infect Dis Clin North Am*. 2000;14: 851–178.
40. Caron-Debarle M, Boccara M, Lagathu F. Adipose tissue as a target of hiv-1 antiretroviral drugs. potential consequences on metabolic regulations. *Curr Pharm Des*. 2010;16:3352–3360.
41. Vidal F, Gutierrez F, Gutierrez M. Pharmacogenetics of adverse effects due to antiretroviral drugs. *AIDS Review*. 2010;12:15–30.
42. Kartsonis NA, D'Aquila RT. Clinical monitoring of HIV-1 infection in the ERA of antiretroviral resistance testing. *Infect Dis Clin North Am.* 2000;14:879–899.
43. Richman DD. HIV chemotherapy. *Nature*. 2001;410:995–1001
44. Gulick, Roy MMD, Mellors, JW, Havlir D, Eron, JJ, Gonzalez C, et al. "Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy", *The New England journal of medicine* 1997;337: 11 734-739.
45. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy *AIDS* 1999, 13:1933–1942
46. Smyth RP, Davenport MP, Mak JM. The origin of genetic diversity in HIV-1. Virus Research. 2012; 169: Pages 415–429
47. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007 Aug;120(8):713-9.
48. Piomboni, P, Baccetti, B. Spermatozoon as a vehicle for HIV-1 and other viruses: a review. Molecular Reproduction and Development. 2000 56: 238–242.
49. Gadella B M, Hammache D, Pieroni G, Colenbrander B, van Golde LM Fantini J. Glycolipids as potential binding sites for HIV: topology in the sperm plasma membrane in relation to the regulation of membrane fusion. Journal of Reproductive Immunology. 1998; 41: 233–253.
50. Muciaccia B, Padula F, Gandini L, Lenzi A, Stefanini M. HIV-1 chemokine co-receptor CCR5 is expressed on the surface of human spermatozoa. AIDS. 2005; 19, 1424–1426.
51. Fanibunda SE, Velhal SM, Raghavan VP, Bandivdekar AH. CD4 independent binding of HIV gp120 to mannose receptor on human spermatozoa. J Acquir Immune Defic Syndr.

2008; 48(4): 389-97

52. Baccetti B, Benedetto A, Burrini AG, Collodel G, Ceccarini EC, Crisa N. HIV-particles in spermatozoa of patientswith AIDS and their transfer into the oocyte. The Journal of Cell Biology. 1994; 127, 903–914.
53. Dulioust E, Du AL, Costagliola D, Guibert J, Kunstmann JM, Heard I, et al. Semen alterations in HIV-1 infected men. Hum Reprod. 1998; 17:2112–2118
54. Tachet A, Dulioust E, Salmon D, De Almeida M, Rivalland S, et al. Detection and quantification of HIV-1 in semen: identification of a subpopulation of men at high potential risk of viral sexual transmission. AIDS. 1999; 13, 823–831.
55. Hanabusa H, Kuji N, Kato S, Tagami H, Kaneko S, Tanaka H, et al. An evaluation of semen processing methods for eliminating HIV-1. AIDS. 2000; 14: 1611–1616.
56. Leruez-Ville M, de Almeida M, Tachet A, Dulioust E, Guibert J, Mandelbrot L, et al. Assisted reproduction in HIV-1-serodifferent couples: the need for viral validation of processed semen. AIDS. 2002 Nov 22;16 (17):2267-73.
57. Muciaccia B, Corallini S, Vicini E, Padula F, Gandini L, Liuzzi G, et al. HIV-1 viral DNA is present in ejaculated abnormal spermatozoa of seropositive subjects. Human Reproduction. 2007; 22, 2868–2878.
58. Le Tortorec A, Dejucq-Rainsford N. HIV infection of the male genital tract--consequences for sexual transmission and reproduction. Int J Androl. 2010; 33(1):e98-108
59. van Leeuwen E, Wit F, Prins J, Reiss P, van der Veen F, Repping S. Semen quality remains stable during 96 weeks of untreated human immunodeficiency virus-1 infection. Fertil Steril. 2008; 90: 636–641
60. Wang D, Li L, Xie Q, Hou Z, Yu X, Ma M, et al. Factors affecting sperm fertilizing capacity in men infected with HIV. J Med Virol. 2014; 86(9):1467-72
61. Crittenden JA, Handelsman DJ, Stewart GJ. Semen analysis in human immunodeficiency virus infection. Fertil Steril. 1992; 57:1294–1299
62. Dondero F, Rossi T, D'OYzi G, Mazzilli F, Rosso R, Sarandrea N, et al. Semen analysis in HIV seropositive men and in subjects at high risk for HIV infection. Hum Reprod. 1996; 11:765–768.
63. Krieger JN, Coombs RW, Collier AC, Koehler JK, Ross SO, Chaloupka K, et al. Fertility parameters in men infected with human immunodeficiency virus. J Infect Dis. 1991; 164:464–469
64. Nicopoullos JD, Almeida PA, Ramsay JW, Gilling-Smith C. The effect of human immunodeWciency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing. Hum Reprod. 2004; 19:2289–2297
65. Kehl S, Weigel M, Müller D, Gentili M, Hornemann A, Sütterlin M. HIV-infection and modern antiretroviral therapy impair sperm quality. Arch Gynecol Obstet. 2011;284 (1):229-33.
66. Cardona-Maya W, Velilla P, Montoya CJ, Cadavid A, Rugeles MT. Presence of HIV-1 DNA in spermatozoa from HIV positive patients: changes in the semen parameters. Curr HIV Res. 2009; 7: 418–424.
67. Pavili L, Daudin M, Moinard N, Walschaerts M, Cuzin L, Massip P, et al. Decrease of mitochondrial DNA level in sperm from patients infected with human immunodeficiency virus-1 linked to nucleoside analogue reverse transcriptase inhibitors. Fertil Steril. 2010; 94:2151–2156
68. Diehl S, Vernazza P, Trein A, Schnaitmann E, Grimbacher B, Setzer B, Walker UA. Mitochondrial DNA and sperm quality in patients under antiretroviral therapy. AIDS. 2003; 17:450–451
69. Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nat Med. 1995; 1(5):417–422.
70. Brinkman K, ter Hofstede HJ, Burger DM, Smeitink JA, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS. 1998; 12(14):1735–1744
71. Robbins WA, Witt KL, Haseman JK, Dunson DB, Troiani L, Cohen MS. Antiretroviral therapy effects on genetic and morphologic end points in lymphocytes and sperm of men with human immunodeficiency virus infection. J Infect Dis 2001; 184:127–135.
72. Lambert-Niclot S, Poirot C, Tubiana R, Houssaini A, Soulié C, Dominguez S, et al. Effect of antiretroviral drugs on the quality of semen. J Med Virol. 2011; 83(8):139 1-4.

73. Sharma B. Anti-HIV-1 drug toxicity and management strategies. Neurobehav HIV Med. 2011;3:27–40.
74. Azu OO. Highly active antiretroviral therapy (HAART) and testicular morphology: current status and a case for a stereologic approach. *J Androl*. 2012;33(6):1130–1142.

TABLE 1: Details of classes of antiretroviral drugs

| Drug class | Generic Name | Brand Name | Abbreviation | Date of Approval by US food and drug administration |
|---|---|---|---|---|
| NRTIs | Emtricitabine | Emtriva | FTC | July 2, 2003 |
| | Tenofovir | Viread | TDF | October 26, 2001 |
| | Didanosine | Videx EC | ddI | October 31, 2000 |
| | Abacavir | Ziagen | ABC | December 17, 1998 |
| | Lamivudine | Epivir | 3TC | November17, 1995 |
| NNRTIs | Stavudine | Zerit | d4T | June 24,1994 |
| | Zidovudine | Retrovir | AZT or ZDV | March 19, 1987 |
| | Etravirine | Intelence | ETR | January 18, 2008 |
| PIs | Efavirenz | Sustiva | EFV | September 17, 1998 |
| | Delavirdine | Rescriptor | DLV | April 4, 1997 |
| | Nevirapine | Viramune | NVP | June 21, 1996 |
| | Darunavir | Prezista | DRV | June 23, 2006 |
| | Tipranavir | Aptivus | TPV | June 22, 2005 |
| | Fosamprenavir | Lexiva | FOS-APV | October 20, 2003 |
| Fusion or entry inhibitors | Atazanavir | Reyataz | ATV | June 20, 2003 |
| | Lopinavir | Kaletra | LPV | September 15, 2000 |
| Integrase inhibitors | Amprenavir | Agenerase | APV | April 15, 1999 |
| | Nelfinavir | Viracept | NFV | March 14, 1997 |
| | Indinavir | Crixivan | IDV | March 13, 1996 |
| | Ritonavir | Norvir | RTV | March 1, 1996 |
| | Saquinavir | Invirase | SQV | December 6, 1995 |
| | Maraviroc | Celsentri | MVC | September 18, 2007 |
| | Enfuvirtide | Fuzeon | T-20 | March 13, 2003 |
| | Raltegravir | Isentress | RAL | October 12, 2007 |

Sources: (73, 74)