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HIV-1 Diversity in Tanzania and its Implication toward Development of Effective Vaccines: A Review Article

Elichilia R. Shao[1-4*], Emmanuel G. Kifaro[1-3], James Kimaro[3], John G. Mrema[2,4] Amos O. Mwasamwaja[2,4], Johnstone Kayandabila[2,4] and Balthazar M. Nyombi1[2,3]

[1]*Kilimanjaro Christian Medical Centre, Moshi, Tanzania*

[2]*Kilimanjaro Christian Medical University College, Moshi, Tanzania*

[3]*Molecular Diagnostic Unit, KCMC Clinical Laboratory Moshi, Kilimanjaro, Moshi, Tanzania*

[4]*Image Doctors Organization, Arusha, Tanzania*

[*]**Corresponding author:** Elichilia R. Shao, Kilimanjaro Christian Medical Centre, Moshi, Tanzania, Tel: +255784491622; E-mail: elichilia2004@yahoo.co.uk

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Abstract

Background: Human immunodeficiency viruses (HIV) are characterized by extremely high genetic variability. This extensive heterogeneity resulted from high error rate of reverse transcriptase enzyme in combination with fast turnover of virions among HIV-infected individuals. With geographical distribution of subtypes its evolution and unpredictable process and intermixing of HIV-1 variants is inevitable. Recombinant viruses contribute already substantially to the global pandemic especially in sub-Saharan African. East Africa studies has shown more complex mixture of HIV-1 Subtypes and associated recombinant virus especially in Tanzania.

Objective: To review past and current literature on HIV-1 diversity and challenges emerging toward effective, safe and cheap HIV-1 Vaccine in Tanzania and gives out some recommendations that could help in tackling these challenges.

Methods: A Pub med, HINARI, Springer online archives and Google Scholar literature of publication on HIV-1 Subtypes and Vaccine was performed to identify articles on 'HIV-1 diversity', 'HIV-1 Subtypes', 'HIV-1 and vaccine' , 'HIV-1 Evolution', 'HIV-1 subtypes and vaccine' and HIV-1 diversity and vaccine in Tanzania. Articles resulting from these searches in the articles were reviewed.

Findings: The predominant HIV-1 subtypes across African continent are HIV-1 Subtype C with few cases of Subtypes A in east Africa and recombinant forms in West Africa. In Tanzania the predominant subtype was HIV-1 Subtype A in Northern side compared with HIV-1 subtype C in the western and central part of the country. We also reported few cases of HIV-1 Subtype D and B in the shore of lake Victoria near Uganda border.

Conclusion: With regard to HIV infection, we are facing a unique challenge where by a concept of vaccine as a standalone prevention measure to end the epidemic is unlikely. Therefore it is a high time to join global effort to come up with a new paradigm of joining potentially promising ideas toward effective HIV/AIDS vaccine. In area like Tanzania where HIV-1 is very diverse can be taken as an opportunity to harness the possibility of finding broad neutralizing antibodies across all strains for a good candidate of HIV-1 vaccine.

Keywords: HIV-1 subtypes; HIV-evolution; HIV-1; Genetic variability; Recombinant virus; Neutralizing antibodies; Reverse transcriptase and East Africa

Introduction

The earliest case of HIV-1 infection was identified in 1959 from an adult Bantu male from Kinshasa, the Democratic Republic of the Congo (DRC). It is claimed that this candidate became infected in rural Cameroon and travelled by river to DRC [1]. Furthermore, the evolutionary analyses of phylogenetic data originating from HIV-1 group M in the Congo River basin were linked to the years 1915-1941 [2]. HIV is characterized by a great genetic diversity due to its high mutation rate that occurs during replication. HIV is classified into HIV-1 and HIV-2. HIV-1 is responsible for the AIDS pandemic and HIV-2, a less aggressive virus, is localized in West-Africa. Phylogenetic analysis of the full-length or specific regions of the HIV-1 genome demonstrate a genetic variability which results into classifying the virus into groups M, N, O and P [3]. The pandemic group M is further classified into nine subtypes A, B, C, D, F, G, H, J and K. This diversity has an impact on diagnosis, replication, development of mutations, treatment response as well as the ability to form recombinant viruses during co-infection [4]. Globally, different subtypes of HIV-1 circulate unevenly in different geographical regions. HIV-1 subtype C is predominant in Sub Saharan Africa (SSA), particularly in the southern, central and eastern part of Africa [3].

Drug resistance against viral infection emerge when one or more drug levels concentration which previously was enough to control viral replication is unable to perform the same function. This is the consequences of mutations that occur in the viral proteins targeted by antiviral agents. The following mechanism must be employed for this

phenomenon to develop; HIV is characterized with high levels of viral replication which is accompanied by absence of proof reading of reverse transcriptase enzyme hence diversity of viral strains from single ancestor. Introduction of one mutation for each viral genome transcribed with the very short half-life of the virus been one or two days, hence lots of viral particles must be produced to maintain the infection [5]. These errors lead to base substitutions, duplication, insertion and recombinant quasi species among newly formed virus. Therefore emergency of resistance strains may occur in the matter of weeks and keeps on accumulating over the time. In other scenario substitution of single amino acids can produce high level resistance because minority viral quasi species carrying single mutations may exist even before commencement of treatment [6]. Recombination is the process similar to sexual replication in higher organisms where contents of distinct viral genomes are mixed up and form a new hybrid virus. HIV recombination introduces large genetic alteration very rapidly and in uncontrolled manner. This phenomenon is a driving force in HIV evolution which occurs at the speed of 2.8 crossovers per genome per cycle [5]. This may affect drug susceptibility because within a single host, recombinant may produce variants resistant to HIV-1 specific regimens and immune pressure. Recombinant can be circulating recombinant form (CRFs) or unique recombinant forms (URFs) means recombinant that are transmitted in the population and those in one individual respectively. This phenomenon complicates effort towards development of effective vaccines due to existing diversity [7].

This diversity of HIV-1 has a significant role on its epidemiology and preventive strategies. Among the impact of diversity is sensitivity to antiretrovirals especially for HIV-1 Subtypes with natural occurring mutations in the absence of drugs [8]. This polymorphism has been seen commonly on reverse transcriptase (RT) and protease regions which are responsible for drug susceptibility [9]. With high diversity of virus in West and Central Africa, very few strain have spread with only four principle subtype and at least two Circulating recombinant Forms (CRFs) been responsible to more than 90% of global epidemic [10]. More than 50% of global infection is due HIV-1 Subtype C, where about 15% Subtype A, 12% Subtype B, 5% Subtype G, 2% Subtype D and about 20% being recombinant forms [10,11]. The diversity of Subtypes is very distinctive in such a way that strains belonging to the same subtypes like HIV-1 C from Kenya and HIV-1 from Tanzania can differ by up 20% in their env gene while the different between HIV-1 A and HIV-1 C env differ by 35% [12]. Basing on the different presented and HIV virus is continuously evolving with the possibility of super-infection or co-infection means there is increasing genetic distance between strains and formation of intra-subtypes recombinant forms [11] (Table 1).

Region	Authors/Year of publication	Subtypes/ inter-subtypes	Dominant Subtype
Northern Africa	Karray-Hakim M, et al. (2003) El Sayed N, et al. (2000) Elharti E, et al. (1997)	B, C, A, CRF01_AE, CRF11-cpx and D	B and C
Central Africa	Ndembi N, et al. (2004) Punzi G, et al. (2005) Marechal V, et al. (2005) Anderson J, et al. (2000)	A, B, C, D, CRF06-cpx, CRF11_cpx, CRF06_cpx and F	CRF_cpx
Western Africa	Monlean M, et al. (2011) Tebid DM, et al. ((2009) Takehisa J, et al. (1998) Chaillet P, et al. (2010) Toni T, et al. (2003) Jallow S, et al. (2009)	CRF02-AG, G,A, URF,B, C, D, CRF01-AE and F	CRF02-AG
Eastern Africa	Somi G, et al. (2008) Mosha F, et al. (2011) Nyombi B, et al. (2008) Kiwelu I, et al. (2012) Yirrell D, et al. (2004) Gale Y, et al. (2006) Herbeck J, et al. (2007) Harmers R, et al. (2011) Ssemwanga D, et al. (2011) Arroyo M, et al. (2009) Lihana R, et al. (2009) Kageha S, et al. (2011) Nyageka B, et al. (2011) Elichilia R, et al. (2014)	A, C, D, AD, B, CRF, URF, CD and AG	A and C
Southern Africa	Bussmann H, et al. 2005) Bredell H, et al. 2002) Deho L, et al. 2008) Maldonaldo F, et al. 2009) Scriba T, et al. (2001) Gordon M, et al. (2003)	C, B, G and CFR02-AG	C

Table 1: The degree of HIV-1 Subtypes and inter-subtypes diversity and its diversity in Africa is summarised [8].

HIV-1 Diversity and Vaccine

Literature revealed that HIV-1 diversity is heterogeneous distributed within different geographical locations with different genetic subtypes. This diversity has big impact on transmissibility, pathogenesis, diagnostic methodologies, treatment outcomes, mutations development and the most important is vaccine development [9,13]. The knowledge about effective vaccine to be developed which will be able to elicit cross-protection across subtypes is poorly understood. This knowledge is very crucial for appropriate planning of HIV vaccine trials so for the future vaccine. For the past three decades no one know if an effective vaccine will depend on specific epitopes or protein conformational changes [14]. Although HIV-1 infected individuals can mount new response, there are upcoming insight that mutations escape by virus from CD8+ Cytotoxic T-Cells and neutralizing over time [15]. Furthermore peptides from highly conserved HIV-1 regions among group M sequences which are close related phylogenetically among strains can be a good model for effective vaccine development [16]. In area of HIV-1 Subtype diversity like Tanzania, we can use this opportunity to study different neutralizing antibodies produced from infected individuals to plan a good vaccine which will work out across the Subtypes.

Tanzania among other East African countries has peculiar diversity of HIV-1 including subtype A, C, D and other recombinant strains

such as CRF10_CD which was first documented in Moshi Tanzania [17]. Since envelope gene at V3 loop is the most conserved region is there need for a vaccine which is specific for each HIV subtype. Glycoprotein 120 is responsible for inducing neutralizing antibodies which will cut across the subtypes. The ability of Glycoprotein 120 to induce production of Cytotoxic T lymphocytes against other conserved HIV-1 proteins will be able to cross react and offer a new hope for vaccines [18]. T lymphocytes (CTLs) against gag gene products and other relatively conserved HIV-1 proteins are usually assumed to be more cross-reactive, offering a hope for the development of broadly protective vaccines [18]. The new challenges arriving from HIV-1 strains capable of using both chemokine receptor (CCR5) and Chemokine receptor (CXCR4), therefore there will be a need to develop antibodies capable of neutralizing both X5 and X4 strains [19]. To solve this puzzle we might think of using cocktail vaccines with different antigens from different subtypes to design candidate vaccines which will target specific HIV epitopes.

HIV-1 Diversity in East Africa

Global HIV diversity complexity has profound implication for many aspects of the pandemic. This diversity of strains possesses threats toward HIV diagnosis as well as viral load measurements assays. Finding Ashwin Vasan s from east Africa evidenced on how different strains has different disease progression and even transmission capacity [20]. Basing on current phylogenetic analysis HIV-1 has been classified into four groups: main group (M), outlier group (O), non-M-non-O (N) group and newly group P [20]. Group M is responsible for the majority of HIV-1 infections globally and is divided into nine genetic subtypes (A, B, C, D, F, G, H, J, and K) [21]. To date HIV-1 subtypes A and C are the most prevalent in the worldwide epidemic. Furthermore HIV-1 subtypes A and F are further subdivided into sub-types A1-A4 and F1-F2 [22]. Of more interest viruses from different lineages within group M are able to recombine during infection and form recombinant viruses [23,24]. Currently more 60 circulating recombinant forms (CRFs) and a large number of unique recombinant forms (URFs) have been described [25], providing evidence for ongoing evolution of HIV-1 in the global epidemic [11]. Furthermore, individuals infected with multiple HIV-1is well as individuals infected with multiple strains of the same HIV-1 subtype have been reported [26]. Increasing national HIV-diversity has brought in profound implication for many aspects of HIV pandemic and possess great challenges for global HIV prevention efforts. In order to define a new subtype, sub-subtype or CRF, representative strains must be identified in at least three individuals with no direct epidemiological linkage [27]. Three near full-length genomic sequences are preferred, but two complete genomes in conjunction with partial sequences of a third strain are sufficient to designate a new subtype, sub-subtype or CRF (to define a CRF, the partial sequence(s) must also confirm the CRFs mosaic structure [28].

In our neighbour country Kenya, HIV-1 Subtype A is the most prevalent strain especially in Southern part of the country. Other subtypes are C, D and G with other recombinant which account for about 30% [29]. The origin of HIV-1 Subtype G is believed to be introduced into Kenya from West Africa through Lake Victoria shore near Uganda. There are two different epidemic of HIV-1 subtype C, there is Subtype C of Indian origin introduced to Kenya through Ethiopia while the second epidemic is Subtype C of South African origin introduced through Tanzania [30]. Other strains seems to be from West Africa where by evidence of HIV-1 patients at Kilifi basing on Phylogenetic analyses of more than 153 pol sequences showed resembling sequences from other part of West Africa, with evidence of one ancestral founder virus. In Rwanda there are very limited information on HIV-1 diversity which might be due to civil war and 1994 genocide. The available few studies among pregnant women attending antenatal clinics showed the dominant Subtypes were A and C. Likewise Burundi, there are very few data on HIV-1 Subtype distribution in the country. Study which was done among infected children at Bujumbura showed that the dominant Subtypes is HIV-1 Subtype C which seems to be introduced from Democratic Republic of Congo (DRC) [8].

Uganda has special interest on HIV-1 Subtypes in East Africa because the fact that first HIV/AIDS case in the region was identified in Kasensero and Lukunyu fishing villages in Rakai, Uganda [8]. Since then intensive studies and preventive measures toward control of the epidemic has been long time started in the country. Those efforts showed significant decrease of epidemic from 14% in 1990 to 8% in 1999, but in the past two years the epidemic started to rise again. Phylogenetic data from those studies showed that Subtype A and D are dominant among others. Subtype D is believed to be originated from central Africa. The prevalence of HIV-1 Subtype D started to decrease around 1990 which might be explained by fast disease progression, this was replaced with increase of A/D recombinant which is less virulence when compared to pure Subtype D [31]. In Tanzania the most dominant Subtypes are A and C where Subtype C is believed to be originated from South Africa through Lubumbashi in DRC. This also explains why most of western part of Tanzania, Mbeya among other region is dominated by HIV-1 Subtype C compared with Northern Tanzania where A seems to dominate. In East Africa, Tanzania is leading for the presence of different recombinant viruses; it is the place where CRF10_CD was reported for the first time among HIV-1 infected infants in Dar es Salaam [32].

HIV-1 Diversity in Tanzania

Studies from Tanzania evidenced on how different strains has different disease progression and even transmission capacity [3]. It is one of the countries in SSA that has been severely affected by the HIV epidemic. Molecular epidemiological studies have reported that HIV-1 subtypes A1, A2, C, D, G, CRF10_CD and other inter-subtype recombinant viruses are circulating in Tanzania [13,23,33]. HIV-1 subtypes A1, A2, C, D, CRF10_CD and other inter-subtype recombinant viruses were reported among bar and hotel workers in Moshi town at Kilimanjaro region [24]. The HIV-1 subtype profile was almost similar with Mbeya region except HIV-1 subtype A2 and CRF10_CD which have not been found in the region [13] (Table 2). Furthermore, HIV-1multiple variants were reported in almost quarter of a high-risk population of female bar and hotel workers with acute HIV-1 infection in the Mbeya region of Tanzania. It is possible that female commercial sex workers and their male clients, as well as female bar and hotel workers, contribute substantially to the rapid expansion of the HIV-1 epidemic in developing countries like Tanzania [11]. These populations may play an important role in evolution facilitating multiple infections and recombination events [13]. The current work which was done in Mwanza Tanzania showed low prevalent of recombinant comparing to the previous studies [33]. This study pointed out the predominant HIV-1 subtypes was A and C which is similar to the previous work from Kilimanjaro by Ireen and Nyombi [11,23]. When we combine all information from these studies in different part of Tanzania we are getting groundwork for the future

HIV-1 vaccine in the region. Diversity of studied population from this region provides future perspectives toward exploration of the efficiency set up for the specific HIV vaccine candidate which will be cut across the diversity of HIV-1 strains at large. Apart from challenges posed from published work on the difficulties to come out with Vaccine which will cover across the diversity of viruses, the other way it may increase the chance of using different HIV-1 strains to come up with the broad neutralizing antibodies.

Region	Authors/Year of publication	Subtypes/ inter-subtypes	Dominant Subtype
Lake(Kagera, Mwanza, Geita, Singida and Shinyanga)	Kasang C, et al. (2012) Kapiga S, et al. (2002) Nyombi B, et al. (2008)	A, B, D, CRF10-CD and recombinant A/D	A
Southern Highlands(Katavi, Rukwa and Mbeya)	Arroyo M, et al. (2004) Arroyo M, et al. (2005) Herbinger K, et al. (2006)	A, C, D, AC, CD, B and CRF10-CD	C and AC
Central (Manyara, Singida and Dodoma)	Johannessen A (2009) Johannessen A (2010) Clara B, et al. (2010)	A, C, D and CRF01-AE	A
Northern (Arusha, Kilimanjaro and Tanga)	Kiwelu I, et al. (2005) Kiwelu I, et al. (2012) Nyombi B, et al. (2008) Elichilia S, et al. (2014)	A, C, AD, D and CRF10-CD	A A A
Eastern (Pwani, Morogoro and Dar es salaam)	Somi G, et al. (2008) Mc Cutchen F, et al. (2005) Mosha F, et al. (2011)	A, C, D, C/A, CRF08-BC/C, D/CRF10-CD, A/D, CRF15-01B/A and C/D	A and C
Southern (Lindi and Mtwara)			No data
Southern Highlands (Ruvuma, Njombe and Iringa)			No data
Western (Kigoma and Tabora)			No data

Table 2: Summary of different studies on HIV-1 diversity in Tanzania (1985-2014) [13,23,24,33-45].

Scientific Challenges toward HIV Vaccine

The forefront reasons for the difficulties towards HIV vaccine development can be summarized below. First, nobody has ever recovered from HIV infection except Timothy Ray Brown 'Berlin patient' therefore natural mechanism to imitate and produce vaccine which will be potent across subtypes and all recombinant forms. Secondly no good animal models to use in experiments, because monkeys are mostly similar but not identical to human beings. Thirdly, HIV integrate its genetic materials into human host cells and destroys the immune system cells that are responsible to fight against it without being noticed by immune surveillance cells. Fourthly, HIV is highly variable; constantly changing therefore it is difficult to find a vaccine which will have the same effects across changing strains. Fifthly, scientific community miss the link or understanding of immune response responsible to protect people against HIV/AIDS.

Conclusion

In this review, we explored HIV-1 diversity and its challenges towards effective vaccine across the available viral strains in Tanzania. For the past three decades new ideas, new minds and its implication with use of automated high technology has made it possible to study HIV molecular diversity, mutations and new drugs towards its eradication. With some promising vaccine trial findings such asRV144 among others, means there are chance to achieve up to 50% protection. For example RV144 trial which involved boosting immunity with an avipox vector (ALVAC) together with gp 120 protein domain which showed that volunteers in vaccine arm acquired 31% fewer HIV-1 infections than individuals in the placebo arm.We are not yet about to celebrate the victory on HIV epidemic eradication due to more challenges toward effective vaccine. With regard to HIV infection, we are facing a unique challenge where by a concept of vaccine as a standalone prevention measure to end the epidemic is unlikely. Envelope gene has an advantage of evading host immune recognition through its sequence diversity which gives it protein conformational flexibility. With its diversity HIV-1 has been difficult to classify by traditional serotyping which means the ordinary approaches to good vaccine candidate in unlikely so far. But the approach of looking for broad neutralizing antibodies among individuals who have controlled infection should not be ignored.

Therefore it is a high time to join global effort to come up with a new paradigm of joining potentially promising ideas toward effective HIV/AIDS vaccine. In area like Tanzania where HIV-1 is very diverse can be taken as an opportunity to harness the possibility of finding broad neutralizing antibodies across all strains.

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References

1. Motulsky AG, Vandepitte J, Fraser GR (1966) Population genetic studies in the Congo. I. Glucose-6-phosphate dehydrogenase deficiency, hemoglobin S, and malaria. Am J Hum Genet 18: 514-537.
2. Rambaut A, Posada D, Crandall KA, Holmes EC (2004) The causes and consequences of HIV evolution. Nat Rev Genet 5: 52-61.
3. Robertson DL, Anderson JP, Bradac JA, Carr JK, Foley B,, et al. (2009) HIV-1 Nomenclature Proposal, A Reference Guide to HIV-1 Classification. Nature review 2: 292-505.
4. Bártolo I and Taveira N (2012) HIV-1 Diversity and Its Implications in Diagnosis, Transmission, Disease Progression, and Antiretroviral Therapy. Retro J 12 7: 172-214.
5. Coffin JM (1995) HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. Science 267: 483-489.

6. Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, et al. (2002) Antiretroviral-drug resistance among patients recently infected with HIV. N Engl J Med 347: 385-394.
7. Carr JK (2006) Viral diversity as a challenge to HIV-1 vaccine development. Curr Opin HIV AIDS 1: 294-300.
8. Lihana RW, Ssemwanga D, Abimiku A, Ndembi N (2012) Update on HIV-1 diversity in Africa: a decade in review. AIDS Rev 14: 83-100.
9. Rhee SY, Liu TF, Kiuchi M, Zioni R, Gifford RJ, et al. (2008) Natural variation of HIV-1 group M integrase: implications for a new class of antiretroviral inhibitors. Retrovirology 5: 74.
10. Velasco-de-Castro CA, Grinsztejn B2, Veloso VG, Bastos FI, Pilotto JH, et al. (2014) HIV-1 diversity and drug resistance mutations among people seeking HIV diagnosis in voluntary counseling and testing sites in Rio de Janeiro, Brazil. PLoS One 9: e87622.
11. Kiwelu IE, Novitsky V, Margolin L, Baca J, Manongi R, et al. (2012) HIV-1 subtypes and recombinants in Northern Tanzania: distribution of viral quasispecies. PLoS One 7: e47605.
12. Wainberg MA, Brenner BG (2012) The Impact of HIV Genetic Polymorphisms and Subtype Differences on the Occurrence of Resistance to Antiretroviral Drugs. Mol Biol Int 2012: 256982.
13. Herbinger KH, Gerhardt M, Piyasirisilp S, Mloka D, Arroyo MA, et al. (2006) Frequency of HIV type 1 dual infection and HIV diversity: analysis of low- and high-risk populations in Mbeya Region, Tanzania. AIDS Res Hum Retroviruses 22: 599-606.
14. Ssemwanga D, Nsubuga RN, Mayanja BN, Lyagoba F, Magambo B, et al. (2013) Effect of HIV-1 subtypes on disease progression in rural Uganda: a prospective clinical cohort study. PLoS One 8: e71768.
15. Cohen MS, Gay CL, Busch MP, Hecht FM (2010) The Detection of Acute HIV Infection. J infect Dis 202: S270-277.
16. Jason T (2010) Super-infection with Multiple CD8+ T Cell Escape Variants of Simian Immunodeficiency Virus. AIDS rev.
17. Kiwelu IE, Renjifo B, Chaplin B, Sam N, Nkya WM, et al. (2003) HIV type 1 subtypes among bar and hotel workers in Moshi, Tanzania. AIDS Res Hum Retroviruses 19: 57-64.
18. Chakrabarti BK, Kong WP, Wu BY, Yang ZY, Friborg J, et al. (2002) Modifications of the human immunodeficiency virus envelope glycoprotein enhance immunogenicity for genetic immunization. J Virol 76: 5357-5368.
19. Montefiori DC, Safrit JT, Lydy SL, Barry AP, Bilska M, et al Induction of Neutralizing Antibodies and Gag-Specific Cellular Immune Responses to an R5 Primary Isolate of Human Immunodeficiency Virus Type 1 in Rhesus Macaques. J Virol 75: 5879-5890.
20. Vasan A, Renjifo B, Hertzmark E, Chaplin B, Msamanga G, et al. (2006) Different rates of disease progression of HIV type 1 infection in Tanzania based on infecting subtype. Clin Infect Dis 42: 843-852.
21. Vallari A, Holzmayer V, Harris B, Yamaguchi J, Ngansop C, et al. (2011) Confirmation of putative HIV-1 group P in Cameroon. J Virol 85: 1403-1407.
22. Thomson MM, Nájera R (2005) Molecular epidemiology of HIV-1 variants in the global AIDS pandemic: an update. AIDS Rev 7: 210-224.
23. Nyombi BM, Holm-Hansen C, Kristiansen KI, Bjune G, Müller F (2008) Prevalence of reverse transcriptase and protease mutations associated with antiretroviral drug resistance among drug-naïve HIV-1 infected pregnant women in Kagera and Kilimanjaro regions, Tanzania. AIDS Res Ther 5: 13.
24. Kiwelu IE, Koulinska IN, Nkya WM, Shao J, Kapiga S, et al. (2005) Identification of CRF10_CD viruses among bar and hotel workers in Moshi, Northern Tanzania. AIDS Res Hum Retroviruses 21: 897-900.
25. http://www.hiv.lanl.gov.
26. Kiwanuka N, Robb M, Laeyendecker O, Kigozi G, Wabwire-Mangen F, et al. (2010) HIV-1 viral subtype differences in the rate of CD4+ T-cell decline among HIV seroincident antiretroviral naive persons in Rakai district, Uganda. J Acquir Immune Defic Syndr 54: 180-184.
27. Renjifo B, Gilbert P, Chaplin B, Vannberg F, Mwakagile D, et al. (1999) Emerging recombinant human immunodeficiency viruses: uneven representation of the envelope V3 region. AIDS 13: 1613-1621.
28. Martine P (2013) Recombinant HIV sequences: their role in the global epidemic. HIV Sequence database.
29. Dowling WE, Kim B, Mason CJ, Wasunna KM, Alam U, et al (2010) Forty-one near full-length HIV-1 sequences from Kenya reveal an epidemic of subtype A and A-containing recombinants. AIDS 16: 1809-1820.
30. Taylor BS, Sobieszczyk ME, McCutchan FE, Hammer SM (2008) The challenge of HIV-1 subtype diversity. N Engl J Med 358: 1590-1602.
31. Kiwelu IE, Nakkestad HL, Shao J, Sommerfelt MA (2000) Evidence of subtype B-like sequences in the V3 loop region of human immunodeficiency virus type 1 in Kilimanjaro, Tanzania. AIDS Res Hum Retroviruses 16: 1191-1195.
32. Njai HF, Ewings FM, Lyimo E, Foulongne V, Ngerageza D3, et al. (2013) Deciphering the complex distribution of human immunodeficiency virus type 1 subtypes among different cohorts in Northern Tanzania. PLoS One 8: e81848.
33. McCutchan FE, Hoelscher M, Tovanabutra S, Piyasirisilp S, Sanders-Buell E, et al. (2005) First In-Depth Analysis of a Heterosexually Acquired HIV-1 Superinfection: Evolution, Temporal Fluctuation, and Inter-Compartment Dynamics from the Seronegative Window Period Through 30 Months Post-Infection. J Virol 79: 11693-11704.
34. Kapiga SH, Sam NE, Shao JF, Renjifo B, Masenga EJ, et al. (2002) HIV-1 epidemic among female bar and hotel workers in northern Tanzania: risk factors and opportunities for prevention. J Acquir Immune Defic Syndr 29: 409-417.
35. Arroyo MA, Hoelscher M, Sanders-Buell E, Herbinger KH, Samky E, et al. (2004) HIV type 1 subtypes among blood donors in the Mbeya region of southwest Tanzania. AIDS Res Hum Retroviruses 20: 895-901.
36. Arroyo MA, Hoelscher M, Sateren W, Samky E, Maboko L, et al. (2005) HIV-1 diversity and prevalence differ between urban and rural areas in the Mbeya region of Tanzania. AIDS 19: 1517-1524.
37. Somi GR, Kibuka T, Diallo K, Tuhuma T, Bennett DE, et al. (2008) Surveillance of transmitted HIV drug resistance among women attending antenatal clinics in Dar es Salaam, Tanzania. Antivir Ther 13 Suppl 2: 77-82.
38. Kasang C, Kalluvya S, Majinge C, Stich A, Bodem J, et al. (2011) HIV drug resistance (HIVDR) in antiretroviral therapy-naive patients in Tanzania not eligible for WHO threshold HIVDR survey is dramatically high. PLoS One 6: e23091.
39. Johannessen A, Holberg-Petersen M, Lovgaarden G, Naman E, Ormaasen V, et al. (2010) HIV type-1 drug resistance testing on dried blood spots is feasible and reliable in patients who fail antiretroviral therapy in rural Tanzania. Antivir Ther 15: 1003-1009.
40. Johannessen A, Garrido C, Zahonero N, Naman E, de Mendoza C (2011) HIV-1 drug resistance testing from dried blood spots collected in rural Tanzania using the ViroSeq HIV-1 Genotyping System. J Antimicrob Chemother 66: 260-264.
41. Bratholm C, Johannessen A, Naman E, Gundersen SG, Kivuyo SL, et al. (2010) Drug resistance is widespread among children who receive long-term antiretroviral treatment at a rural Tanzanian hospital. J Antimicrob Chemother 65: 1996-2000.
42. Mosha F, Urassa W, Aboud S, Lyamuya E, Sandstrom E, et al. (2011) Prevalence of genotypic resistance to antiretroviral drugs in treatment-naive youths infected with diverse HIV type 1 subtypes and recombinant forms in Dar es Salaam, Tanzania. AIDS Res Hum Retroviruses 27: 377-382.
43. Shao E, Kifaro EG2, Chilumba IB2, Nyombi BM3, Moyo S4, et al. (2014) HIV-1 drug mutations in children from northern Tanzania. J Antimicrob Chemother 69: 1928-1932.
44. Kwong PD, Mascola JR, Nabel GJ (2011) Rational design of vaccines to elicit broadly neutralizing antibodies to HIV-1. Cold Spring Harb Perspect Med 1: a007278.

45. Eller MA, Slike BM, Cox JH, Lesho E, Wang Z, et al. (2011) A double-blind randomized phase I clinical trial targeting ALVAC-HIV vaccine to human dendritic cells. PLoS One 6: e24254.