OPPORTUNISTIC VIRUSES OF HIV INFECTION

BY

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Chapter One

INTRODUCTION

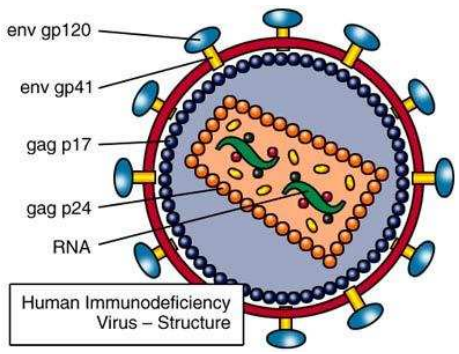
An Opportunistic infection is an infection caused by a pathogen or groups of pathogen appropriately termed “Opportunistic“, because they are normally non-pathogenic in an immunocompetent individuals but becomes pathogenic to an immunocompromised persons (i.e immune suppressed individuals).Opportunistic pathogens like some types of viruses are microorganisms that cause diseases only when introduced into an unusual location/environment such as in an immunologically suppressed individuals (Obireh omokaroh, 2012).Viruses are minute infectious agents with a core genetic material (DNA or RNA) enclosed in a protein shell called capsid which causes disease by invading host’s cell and commandeering the host cell’s synthetic capabilities to produce more viruses instead of host cell’s genes (Cheesbrough, M. 2000). An example of opportunistic virus is the herpes virus specie called Herpes Simplex Virus type-1 and type-2 (HSV-1 & HSV-2) also known as Herpes Human Virus; type-1 and type-2 which causes cold sores and genital sores respectively. Other Opportunistic Viruses also

exists especially those in the Herpes Viridae family for example, the Cytomegalovirus (CMV), which causes a form of congenital disease and the Varicella Zoster Virus (VZV), which causes chicken pox disease and shingles disease.

THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) AS A PRIMARY INFECTION.

In every Opportunistic infection, there must be some host predisposing factors which are infected by primary pathogens. Prior infection such as HIV infections serves as a primary pathogenic infection which invades the suscAeptible host's Immune (defense) system and creates a conducive environment for later proliferation the "Opportunistic Viruses" (Abbey, 1995). The Infection of HIV causes steady depletion of its host blood lymphocytic cells (T-Helper cells in particular) which is a type of white blood cell commonly called CD4 cells which its main function is to wade-off invading pathogens (Cheesbrough, M. 2000). The depleting action of HIV on its Host, thus culminates into the state of advanced immune deficiency known as "Acquired Immune Deficiency Syndrome (AIDS) which is a disease characterized by reducing the CD4 cells count to less than

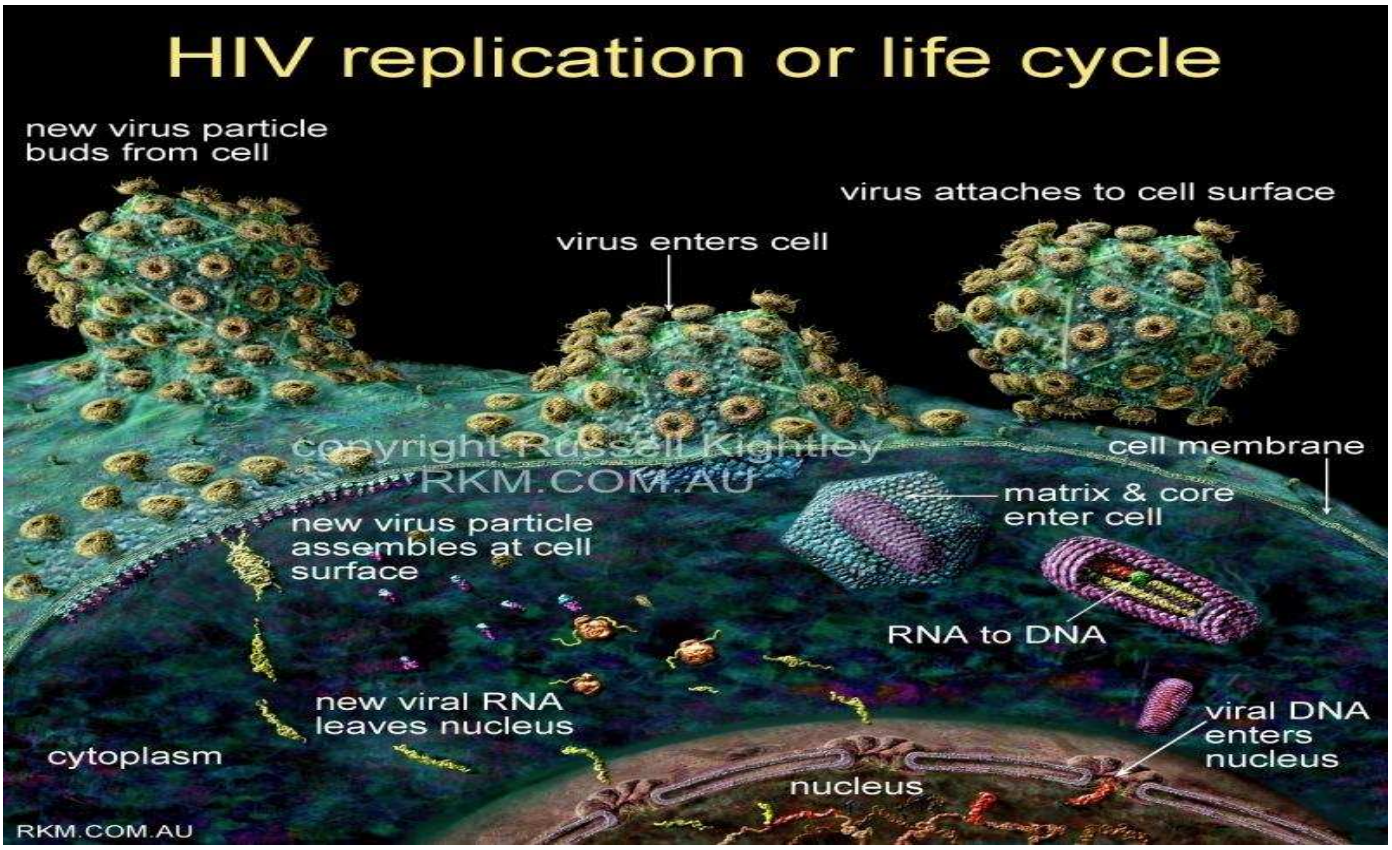
250/ml-200/ml of blood so that the CD4 won't be enough to combat invading pathogens, thereby encouraging the proliferations of these so called "Opportunistic Viruses" being mentioned earlier above.



"THE STRUCTURE OF HIV-1 VIRION" .

High resolution electron microscopy has revealed that HIV-virion has an icosahedral nucleocapsid which is enveloped with spikes. These spikes are formed by the two major viral-envelope proteins (i.e. gp120 and gp41 env.).The P7 protein binds directly to the genomic RNA through a zinc-finger structural motif and together with P9, forms the nucleoid core. Importantly, this retroviral core also contains two copies of the single-stranded HIV-1 genomic RNA that is associated with the various preformed viral enzymes, including the reverse transcriptase, integrase and protease.

The life Cycle of the Human Immuno Deficiency Virus (HIV-1)



The cycle involves seven stages

1. Attachment of the virion
2. Internalization of the virion
3. Reverse transcription and integration
4. Viral latency
5. Early expression of the HIV-1 regulatory genes
6. Late expression of the HIV-1 structural and enzymatic genes
7. Morphogenesis of the HIV-1 virion.

Major activities at each of this seven (7) stages of HIV-I life cycle are as follows;

1. **Attachment of the Virion:** Since viruses exhibits tropism, (i.e. different viruses have affinity for different cells and organs of the body).The human CD4, lymphocyte and monocyte are the major cellular targets for HIV-I infection. At this stage, the HIV-1 gp20 envelope protein binds to CD4 with strikingly high affinity.
2. **Internationalization of the Virion:** The receptor bound human immunodeficiency virus (HIV-I) virions are brought inside the cell by either classic receptor-mediated endocytosis or virus mediated membrane fusion. This is the apparent vulnerable stage of the life cycle of HIV-1.
3. **Reverse Transcription and Integration:** (The replicative stage).The viral replication starts with generation of the 1st - strand DNA copy of the viral RNA mediated by the HIV-I encoded reverse transcriptase. When completed, the reverse-transcription reaction yields a double-stranded DNA replica of the original RNA genome containing tandem long terminal

repeats at each end of the DNA in lieu of the short terminal repeats present at the RNA level.

4. **Viral Latency:** After entry into the CD4+ cell, HIV-I may establish a latent or persistent form of infection. Some latent diseases like progressive dementia and diarrhea wasting syndrome may begin to manifest.
5. **Early Expression of HIV-1 Regulatory Genes**: At this stage, there is binding of inducible and constitutive host transcription factors to sites in the HIV-I long terminal. The initial population of genomic-length viral messenger mRNA molecules reaches the cytoplasm. (i.e, Synthesis of early regulatory gene starts here).
6. **Late Expression of the HIV-I Structural and Enzymatic Genes**: HIV-I viral proteins are uniquely encoded by incompletely processed viral transcripts, including the unspliced gap-pol mRNA and the single spliced envelope mRNA. This is the stage of late structural gene synthesis. Here, there is transition between the synthesis of early regulatory gene to late structural gene.

7. **Morphogenesis of the HIV-I Virion:** Assembly of the infectious HIV-I virion proceeds in a stepwise manner, initially involving aggregation of the ribonucleo-protein core in the cytoplasm. Once assembled, these cores move to the surface and bud through the plasma membrane. It is during this final budding process that the cleavage events mediated by HIV-I protease occur, as well as the myristylation of the p17 Gag protein.

PATHOGENIC ASPECTS OF HIV DISEASE (AIDS)

HIV infects two key cells of the immune system: namely; the CD4 + (T-helper = "TH Cells") lymphocytes and the antigen presenting cells, including: macrophages, dendritic cells, follicular dendrite cell and related cells. CD4 lymphocytes are rapidly eliminated after they have become infected by viral cytopathic effects or host-mediated cytotoxic mechanism or both. The gradual spread to increasing numbers of these cells leads to progressive depression of this central cell of immune responses.The killing of the critical CD4+ subset of human T-cells that is induced by HIV-I squarely underlies the profound immune deficiency so characteristic of advanced AIDS.The depletion action of HIV virus

thus culminates into the advanced state of immunodeficiency known as Acquired Immune Deficiency Syndrome (AIDS). AIDS disease is clinically manifested by reducing the CD4 cells count to less than 250/ml – 200/ml of blood serum lymphocytes so that it would not be enough to combat invading pathogens, thereby encouraging the proliferations of some opportunistic viruses.

Picture of a patient suffering from HIV AIDS

CHAPTER TWO

LITERATURE REVIEW

2.0 THE OPPORTUNISTIC VIRUSES OF HIV INFECTION

In situations of immunodeficiency such as the one brought about by AIDS, certain viruses that takes this opportunity to invade the body defense system and cause diseases are thus called "Opportunistic Viruses"

2.1 Classification Of The Opportunistic Viruses.

GROUP - Group-1 (double-stranded DNA)

ORDER - HerpesVirales

FAMILY - Herpesviridae

SUB-FAMILY - AlphaHerpesvirinae

GENUS - Herpes Simplex Virus

SPECIES - Herpes Simplex Virus, type-1(HHV-1) and Herpes Simplex Virus, type-2 (HHV-2).

Imeda P.E et al,. (2008) worked on a total of 620 HIV positive children 0-5 years attending University of Benin Teaching Hospital, Benin City, were examined in this study. They were grouped into less than 1 year and 1-5 years based on CDC classification system. 218 children were under 1 year and 402 were 1-5 years. The overall results showed that malaria infection recorded the highest prevalence with 71.10% in less than 1 year and 76.37% in 1-5 years. This was followed by Oral Candidiasis 38.07% in less than 1 year and 50% in 1-5 years. Bacteraemia had 23.40% and 30.60% in less than 1 year and 1-5 years respectively. Diarrhoea, 14.22% in less than 1 year and 17.66% in 1-5 years. Otitis media had 10.55% and 10.95% in less than 1 year and 1-5 years respectively. Similarly, 590 apparently healthy HIV-negative children within the same age group were evaluated for the presence of these infections. There was a statistical significance between opportunistic infections and HIV infection ($P < 0.001$). Malaria infection was the most prevalent opportunistic infection in this population and may probably be due to environmental condition of this locality as well as the low immune status of the children.

Harvey and Lee (1982) worked on the human immunodeficiency virus (HIV) infection leading to Acquired Immunodeficiency Syndrome (AIDS) causes progressive decline in immunological response in people living with HIV/AIDS (PLWHA) making them susceptible to a variety of and opportunistic infections which are responsible for morbidity and mortality. Community Care Centres (CCC) have been started as a measure to ensure compliance of antiretroviral treatment. Detailed history taking, clinical examination and laboratory tests were carried out in 110 patients.The pattern of opportunistic infections in people living with HIV/AIDS (PLWHA) attending CC was studied. The presenting symptoms were fever (82.2%), weight loss (65.8%), cough and dyspnoea (45.5%) and diarrhoea (41.7%). One or more opportunistic infections were observed in 63 patients (57%). Commonly observed were pulmonary tuberculosis (52.3%), candidiasis (39%), cryptosporidial diarrhoea (30.1%) and Pneumocystis Carinii Pneumonia (PCP) (14.2%). In 46.4% of cases CD4 count was less than 200. Findings point to the importance of early diagnosis and treatment of opportunistic infections in order to improve quality and expectancy of life.

Pneumocystis jirovecii (previously *Pneumocystis carinii*1 is a fungus2 that is ubiquitous. It is unclear whether infection occurs as a primary event3 or as a result of colonisation with reactivation, although antibodies against the organism are present in more than 85% of children under three years of age, suggesting that reactivation with immunosuppression occurs. *P. jirovecii* pneumonia (PJP), is still the most common AIDS defining condition, and is usually seen in people presenting late in the course of HIV infection6 or in people with poor adherence to PJP prophylaxis or combination antiretroviral therapy (cART). PJP occurs uncommonly in persons with a CD4 cell count greater than 200 cells/μL, or 14% of the total lymphocyte count, although cases have been reported in individuals with more preserved immune function.7 HIV RNA viral load (VL) has been shown to increase during opportunistic illnesses (OIs), suggesting active HIV replication in response to infection among patients not taking antiretroviral therapy (ART).We assessed the effects of OIs on HIV RNA VL and CD4_ T cell counts among patients on ART with initially suppressed VL. Bradley and Morris (1986).

CHAPTER THREE

3.0 Disease caused by some opportunistic viruses

Although some of these opportunistic viruses and disease they cause are most peculiar to people with advanced HIV infections (AIDS) they can also cause similar diseases in non-AIDS patients but their presence or manifestations of diseases attributed to these viruses generally indicates a state of immune compromise (i.e weak immunity).

3.1 Cold Sores and Genital Sores Disease

Cold sores and genital sores disease are caused by HHV-I (oral herpes) and HHV-2 (genital herpes) respectively. This is characterized by groups of fluid filled blisters which appear on red swollen areas of the skin or on the mucous membranes. The areas can be tender and painful, the blisters heals without scarring but have a tendency to reoccur.

a) **Etiologic Agent of cold sore** is HHV-1 (human herpes virus type-1 (oral herpes).
b) **Route of transmission of the disease** by close personal contact such as kissing. Adults with these diseases also transit it to babies when they kiss the babies during infanthood.

c) **Epidemiology:** Most people contacts the disease between ages of three and five but will not show any symptoms until after puberty age.About 20 percent of the people with HSV antibodies have recurrent attacks of cold sores throughout their lives.

d) **Prevention and Control Measures:** Naturally or inborn, about 30% of adult population have antibodies against HSV-1 in their blood and around 20% of the adult population have antibodies against HSV type-2.

- Avoid direct contact with sores of a patient, including fingers and genitals.
- Wash your hands after touching the lips.
- Strengthen your body defences by healthy lifestyle such as, eating a varied balanced diet, regular exercise and getting enough sleep.
- Using a sunblock to prevent reactivation of the virus during menstruation, fever and exposure to sunlight (i.e. can cause reactivation).

e) **Symptoms of cold sores:** Primary symptoms varies from mild to no symptom at all (asymptomatic) in some individuals. Symptoms may present as follows:

- Unpleasant tingling feeling in the skin during the 1st - 3 weeks of infection, it subsides spontaneously within a few weeks but a number of fluid blisters appears after a short while.
- The sores become covered by scabs that typically fall off after 8 to 10 days. The virus can spread until the sores are completely covered by scabs.
- In children the virus can infect the mouth and the throat.
- The infection may be accompanied by a fever and general aches and pain.

f) **Diagnosis:** A combination of the patients' medical history and the appearance of the sores is usually sufficient for a diagnosis.

TREATMENT

a) Cold sore is treated with intravenous antiviral medication, such as *acyclovir* 5 percent cream (e.g. zorirax, cold sore cream) which is applied five times a day for five days.
   - The cream can be bought over the counter and treatment should start as soon as first symptoms appears to reduce the length of the outbreak and the infectious period

b) Persistent or recurrent severe attacks can be treated by Anti-HSV agents (e.g. zorirax) in pill form.

3.3 Genital Sores Disease

This is a disease caused by HSV-2 (genital herpes virus) that is passed on during vaginal intermode of course (or anal intercourse) or sometimes transmission during oral sex given to a woman (cunnlingus).

Symptoms: A redish or darkish patch on the genitals or the anus and this is quickly replaced by one or more. In mode of transmission, there is some crossover of between HSV-1 in mouth to the genital during oral sex and HSV-2 in genitals to the mouth too. Blisters, filled with straw-coloured fluid. They may

also be tingling or burning sensation often times, the gland in the grain swells-up.

- Urination can be painful in both sexes but women also has slight purulent odourless discharges when the blisters are present.
- The blisters will then burst and turn into small ulcers which heal after two or three weeks without any scarring.

Diagnosis

If genital sore is suspected, go to a clinic in most cases appearance of blisters will help in the diagnosis and the disease can be confirmed by a viral analysis of the watery fluid in the blister.

Treatment

Use of antiviral cream in first attack and on recurrence, use oral tablets of the antiviral acyclovir (zovirax) given at a dose of 200mg, five times a day for at least five days.

PREVENTION AND CONTROL MEASURES

- Avoid sex during or oral sex especially when a partner has blisters or suspects blister developing around genitals.

- Use a condom for and sex and include dental dam which is a rectangle of material that prevents transmission of the virus during oral sex (cullilingus).
- Use antiviral creams such as zovirax sometimes around genitals.

3.4 Some congenital disease

Signs and symptoms of CMV infection;

Almost 80% of infants born with congenital CMV infection shows no symptom at birth symptoms appears 2 or more years after birth or may not appear at all (asymptomatic) possible signs includes:

i) Premature birth

ii) Liver problems

iii) Lungs problems

iv) Spleen problems

v) Small size at birth

vi) Small head size

vii) Seizures.

Permanent health problems or disabilities due to congenital CMV infection include:

- Loss of hearing, loss of vision
- Mental disability, small head size
- Lack of coordination, seizures
- Death (in rare cases).

Transmission

The viral disease is generally passed from infected person to others through direct contact with body fluids such as urine, saliva or breast milk.Can be spread through transplanted organs and blood transfusions.

EPIDEMIOLOGY

People who are at most risk of contacting congenital CMV are the pregnant women, nursing mothers and those that take care of babies, whose occupation exposes them to contact with urine and saliva of babies. Overall, out of 1,000 live births in Africa , about 8 infants will have congenital CMV infection (less than1%)of which one to two will result to permanent problem (or disability in hearing and loss of vision)

DIAGNOSIS

A person infected with Cytomegalovirus (CMV) will develop antibodies (proteins that indicates prior infection to the virus) that will stay in the person's body throughout life. A blood test can detect those antibodies as confirmatory test that the person has been infected with the CMV infection. Other test involves urine, saliva and other body tissues. Pregnant women infected with CMV, shows symptoms resembling Mononucleosis or Flu-like illness. Infants are routinely tested for CMV within 2-3weeks of birth using their urine, saliva or blood samples.

NB, Antibody test cannot be used to diagnose congenital CMV in infants since their immune system is not yet set to produce any antibody within the 2-3weeks of birth which is usually a period of CMV routine test on infant

PREVENTION AND CONTROL

Pregnant women and baby sitters can reduce the risk of CMV spread by the following hygienic practices;

1) Wash your hands often with soap and water for 15 to 20 seconds, especially after; changing diapers, wiping a young Childs drool or nose, after handling children toys.
2) Also Avoid; sharing food, drinks, or eating utensils used by young children, putting a Childs pacifier in your mouth.
3) Do not share a toothbrush with a young child.
4) Avoid contact with saliva when kissing a child.
5) Clean toys, countertops and other surfaces that come into contact with children urine and saliva.

3.5 CHICKEN POX DISEASE

Chicken pox (Varicella) is an acute febrile illness characterized by a very itchy red skin rash. This disease is one of the most common infectious disease of childhood, but it tends to be more severe on adults than in children.

Etiologic Agent

Chicken pox is cause by the herpes varicella-zoster virus

Route Of Transmission; Chicken pox is transmitted from person to person either through direct contacts with infectious droplets from sneeze or cough or indirectly

through contacts with articles, clothing, bed linens or oozing blisters of an infected person (Boots Web MD Medical 2014).

EPIDEMIOLOGY

- Chicken pox is a cough infection all over the world (ubiquitous in distribution).
- Man is the reservoir of the infection.
- The infected person remains infectious for about one (1) week from the onset of the illness.
- The disease is most contagious at a day or two before the rashes appears and until the rash is completely dry and scabbed over.
- The incubation period is usually from 2 to 3 weeks (before the symptoms starts to manifest).
- The Overall fatality rate is low but high in cases complicated with primary viral pneumonia.

SYMPTOMS OF CHICKEN POX

There is no marked constitutional signs until the rash appears unlike small pox which comes with fever, headache and severe prostration for 2 to 4 days before rash appears.Lasting seven to ten days, the rash progresses from red bumps to a fluid-filled blisters (vesicles) that drain and scab over.The cycle repeats itself in new areas of the body until finally (about 2 weeks) all of the sores have healed, the virus and the disease is contagious until the spots dries up and the rash break off.

DIAGNOSIS OF CHICKEN

In clinical diagnosis for Chicken pox, public health measures are precautionary. Measure should be taken in comparing the symptoms of chicken pox with small pox so that the diagnosis of small pox can be firmly excluded. The organism may be isolated from the early skin lesions or form throat washings, the clinical diagnostic laboratory tests should confirm chicken pox if there is a rising tit of complement-fixing antibodies in acute and convalescent sera.

TREATMENT FOR CHICKEN POX

Most cases of chicken pox require little or no treatment beyond treating the symptoms.

- Use antiviral drug (e.g. acyclovir) to shorten the duration of chicken pox symptoms and persons with weakened immune system can also take this drug.
- Take over the counter drugs to suppress pain, itching and swelling involved with chicken pox.
- Use antibiotics to treat any secondary bacterial infection from chicken pox like bacterial pneumonia.

HOME REMEDIES

- To ease itching, add a handful of oats or baking soda to bath water. Apply cool, wet towels to skin and allow them to dry.
- Dab calamine lotion onto the lesions to relieve itching.
- Remove babies' nappy as much as possible to allow the vesicles to dry out and scab.

PREVENTION AND CONTROL

- Isolate patients of chicken pox to avoid him/her spreading the disease until all of the blisters have burst and crusted over.
- Seek medical attention within 24 hours of the rash appearance.
- Avoid incessant body contacts since infected persons doesn't show signs until rash appears.
- Practice better personal hygiene like hand washing and also eat foods and supplements that will burst your immunity against infections.

3.6 Shingles disease

Shingles is an infection caused by the virus varicella-zoster, which is the same virus that causes chickenpox. Even after chickenpox is treated, the virus may live on in your nerve tissues for years before reactivating as shingles. Shingles may also be referred to as herpes zoster. This type of viral infection is characterized by a red skin rash that usually causes pain and burning. Shingles usually appears as a stripe of blisters on one

side of the body, typically on the torso, neck, or face (CDC, 2011). Most cases of shingles clear up within two to three weeks. Shingles rarely recurs more than once in the same individual.

Etiologic Agent

Chickenpox, also known as varicella, and shingles, also known as herpes zoster, are caused by the varicella zoster virus (VZV), a DNA virus belonging to the herpes virus group. Primary infection with VZV causes chickenpox. Like other herpes viruses, VZV has the capacity to persist in the body as a latent infection after the primary infection has occurred. Shingles results from reactivation of latent infection.

Modes of Transmission

VZV is transmitted from person to person by the following means:

- From chickenpox cases:
- Droplet spread when a person coughs or sneezes.
- Direct contact with upper respiratory secretions or lesions that have not yet crusted over; orAirborne spread.
- Direct contact with lesion.

Epidemiology

Shingles is found worldwide and has no seasonal variation. This disease increases with increasing age and is more common among immunocompromised persons and among children with a history of intrauterine chickenpox or chickenpox occurring within the first year of life. The latter have an increased risk of developing shingles at an early age. Approximately 15% of the general population will experience shingles during their lifetime.

Symptoms of Shingles

The first symptoms of shingles are usually pain and burning. The pain is usually on one side of the body and occurs in small patches. A red rash typically follows.

Rash characteristics include:

- Red patches.
- Fluid-filled blisters that break easily.
- A rash that wraps around from the spine to the torso.
- A rash on the face and ears.
- Itching.

Diagnosis of Shingles

Most cases of shingles can be diagnosed with a physical examination of rashes and blisters. Your doctor may also ask questions about your medical history. Rarely, your doctor may need to test a sample of your skin or the fluid from your blisters. This involves using a sterile swab to collect a sample of tissue or fluid. Samples are then sent to a medical laboratory to confirm presence of the virus.

Treatments for Shingles

There is no cure for shingles, but medication may be prescribed to ease symptoms and shorten the length of the infection.

Medications prescribed for shingles may include:

- antiviral medications, including acyclovir, valcyclovir, and famciclovir (to reduce pain and speed recovery)
- anti-inflammation drugs (to ease pain and swelling)
- narcotic medications or analgesics (to reduce pain)
- anticonvulsants or tricyclic antidepressants (to treat prolonged pain)

- antihistamines, such as Benadryl (to treat itching)
- numbing creams, gels, or patches, such as lidocaine (to reduce pain)
- zostrix cream, which can help reduce the risk of postherpetic neuralgia (nerve pain experienced after recovery from shingles)

Home treatment can also help ease symptoms. Home treatments may include:

- rest
- applying cold wet compresses to the rash to reduce pain
- applying calamine lotion to reduce itching
- taking colloidal oatmeal baths to ease pain and itching.

Shingles typically clears up within a few weeks and rarely recurs.

Prevention of Shingles

Vaccines can help keep you from developing severe shingles symptoms or complications from shingles. All children should receive a chickenpox vaccine, also known as a varicella immunization. Adults who have never had chicken pox should

also get this vaccine. The immunization does not necessarily mean that you won't get chickenpox, but it can help reduce the severity of your symptoms. Adults who are age 60 or older should get a shingles vaccine, also known as the varicella-zoster immunization. This vaccine helps to prevent severe symptoms and complications associated with shingles.Shingles is contagious. If you become infected, certain steps must be taken to prevent spread of the infection.

Preventing the spread of shingles includes:

- keeping your skin clean
- avoiding contact with individuals who have not had chickenpox or who have weakened immune systems
- washing any items you touch with boiling water to kill the virus

Conclusion

Most opportunistic virus of HIV infection are contagious and their side effects are drastic. These could be prevented by practicing good personal hygiene, regular medical checkup, regular exercise, rest and taking of well balanced diet in order to boost the immune system.

References

Leung J, Harpaz R, Molinari NA, et al. Herpes zoster incidence among insured persons in the United States, 1993-2006; evaluation of impact of varicella vaccination. Clin Infect Dis 2011;52:332-40.

Oxman MN. Zoster vaccine: current status and future prospects. Clin Infect Dis 2010;51:197-213.

Tseng HF, Smith N, Sy LS, Jacobsen SJ. Evaluation of the incidence of herpes zoster after concomitant administration of zoster vaccine and polysaccharide pneumococcal vaccine. Vaccine 2011;29:3628-32.

sSeward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. JAMA 2002;287:606–11.

Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases: a household contact study. JAMA 2004;292:704–8.

Shields KE, Galil K, Seward J, et al. Varicella vaccine exposure during pregnancy: data from the first 5 years of the pregnancy registry. Obstet Gynecol 2001; 98:14–19.

Vazquez M, LaRuissa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. JAMA 2004;291:851–92.

Davis MM, Patel MS, Gebremariam A. Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. Pediatrics 2004;114:786–92.

Benson, C.A., Kaplan, J.E., Masor, H., Alice, P. and Holmes, K.K. (2004). Treatment opportunistic infections Among HIV infected Adults and Adolescents: Recommendations and Reports.*Morbidity and Mortality Weekly Report* 53 (RR 15):1-112.

CDC (1994). Revised classification system for HIV in children less than 13 years of age. *MMWR* **43:RR-12.**

CDC (2006). The link between malaria and HIV. Centres for Disease Control, Division of Parasitic Diseases, 13 January, 2006.

Chakraborty, R. and Shingada, D. (2007). Treating opportunistic infections in HIV-infected children (extended). Guidelines for the children's HIV Association (CHIVA)

Cheesbrough, M. (2000). Paediatric HIV disease. District Laboratory Practice in Tropical Countries.Cambridge University Press pp 256.

Constantine, N.T., Saville, R.D. and Dax, E.M. (2005). Retroviral testing and Quality Assurance. *Essentials for Laboratory Diagnosis* pp 56-58.

Cowan, S.T. and Steel, K.J. (1985). Manual for the identification of Medical Bacteria. 4th Ed. London.Cambridge University Press.

Dull, J.S., Sen, P., Raffanti, S. et al. (1991). Oral candidiasis as a marker of acute retroviral illness.*Southern Medical Jounal* 84:744-735, 739.

Merchant, R.H. and Quadir, Z.A. (2002). Management of opportunistic infections in paediatric HIV. *Indian Journal of Paediatric* 69(12):973-977.

Nchabeleng, M., Yeung, S., Escott, S., Wilkinson, D. and Sturm, A.W. (2000). Bacteraemia in HIVinfected children in a rural Kwa-zulu Natal Hospital. Int. Conf. AIDS. July 9-14; 13: abstract No. MoPeB2202.

Onifade, A.K., Akanni, E.O. and Mewoyeka, O.O. (2007). Incidence of Malaria Infection among Human Immunodeficiency Virus patients in Ondo State, Nigeria. *Middle-East Journal of Scientific Research* 2(2):48-53.

WHO (2007). Paediatric HIV and treatment of children living with HIV. Report of the first meeting of the subcommittee of the Expert Committee on the selection and use of Essential Medicine on Children's Medicines. Geneva, 9th – 13th July, 2007.