CLASSIFICATION OF HIV DISEASE IN CHILDREN – TOWARDS PRAGMATISM?

Mark F Cotton, *MB ChB, MMed (Paed), PhD, FCPaed (SA), DTM&H, DCH (SA)*
KID-CRU and Paediatric Infectious Diseases Unit, Tygerberg Children's Hospital, Faculty of Health Sciences, Stellenbosch University

HIV infection is a multisystem disease characterised by progressive immunodeficiency and increasing susceptibility to common and opportunistic pathogens. Progressive disease is characterised by reversible and then permanent end-organ dysfunction due to HIV itself or co-pathogens, and also an increased risk of malignancy.

The hallmark of immunodeficiency is CD4+ lymphocyte depletion, although other elements of the immune system are also deranged. Children with HIV are classified according to clinical and immunological criteria. Both systems are useful for individual patient management, and together are more useful than either parameter individually.

Classification into mutually exclusive categories allows standardisation of this complex multisystem disease process, facilitating case management and informing the clinician of both the extent of clinical progression and prognosis. Because of the varied prevalence of pathogens in different geographical areas, disease manifestations may differ. Some pathogens, such as *Pneumocystis jiroveci* and cytomegalovirus (CMV), will cause the same disease manifestations in any location. Others, such as *Mycobacterium tuberculosis*, are more prevalent in sub-Saharan Africa than elsewhere. A classification system should take cognisance of this variability.

Decisions to initiate antiretroviral therapy (ART) or to change therapy because of regimen failure are based on an understanding of disease progression. Lastly, the classification system allows for surveillance, facilitating planning by ministries of health for adequate resources and equitable access to care.

DIFFERENCES BETWEEN ADULTS AND CHILDREN

As children are growing and developing, many clinical manifestations may be unique to children. Both the immunological system and organs grow and develop in children but are static in adults. The CD4 percentage stays relatively constant, but there is a decline in CD4+ T-cell numbers as children mature. CD4 cells may be functionally immature, most graphically illustrated by the finding of a high
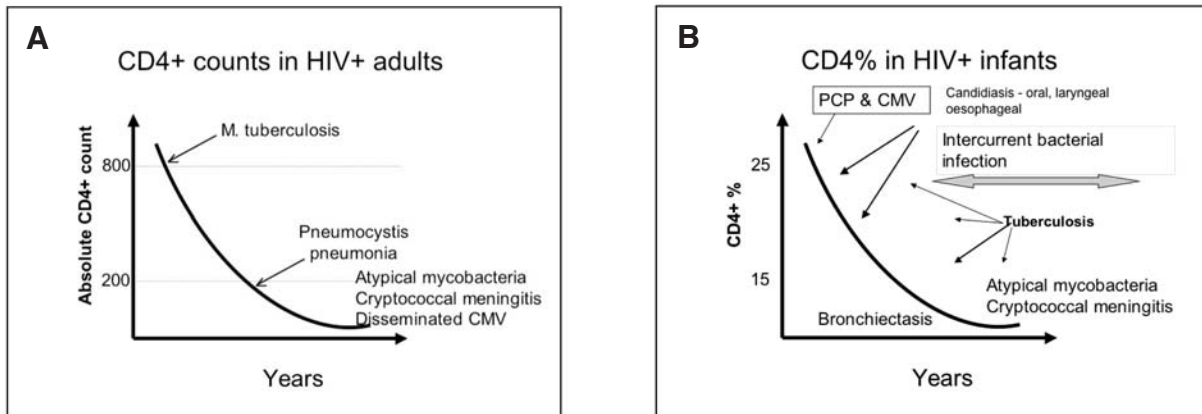
Fig. 1. Relationship between CD4 cells, disease and time in adults (A) and children (B).

prevalence of *Pneumocystis* pneumonia (PCP) in young infants with far higher CD4 counts or percentages than would occur in adults. Age is an important determinant for rapid progression in infants. Conditions such as lymphoid interstitial pneumonitis (LIP) are recognised more commonly in children than adults. Differences in disease manifestation between adults and children are shown in Fig. 1 (A and B). In infants, young age and immunological immaturity are probably the most important determinants of disease.

THE CENTERS FOR DISEASE CONTROL AND PREVENTION CLASSIFICATION

The Centers for Disease Control (CDC) classification was first introduced in 1987 and modified in 1994.[1,2] It comprised clinical and immunological components, recognising that there could be discordance between the two. Such discordance has been shown in South African children.[3]

Clinical categories range from asymptomatic (N) to mild symptoms and signs (A), moderate severity (B) and severe (C) (Table I). Immunological stages range from no CD4+ depletion (stage 1) to moderate depletion (stage 2) and severe depletion (stage 3) (see Table II in the Paediatric ART Guidelines, p. 20).

The classification is well accepted and has shown excellent predictive value, especially in North American and European children. For example, in an analysis for the Pediatric Spectrum of Diseases Project, Barnhart and colleagues could differentiate between the different stages of disease (Table I).[4] In an African setting, although the classification is useful, it is

sometimes difficult to fit symptomatic children into the classification system. For example, in a study from Malawi, because of high mortality by 3 years of age only 10% of children were in stage B or C as the majority had already died.[5]

INCONSISTENCIES

There are a number of inconsistencies in the classification. For example, two episodes of bacterial infection within a 2-year period, responding well to antibiotics, and lymphoma are both classified in C. Leiomyosarcoma is in B, but Kaposi's sarcoma is in C. Congenital CMV or toxoplasmosis are in B, but if of later onset are in C. Congenital or early infection may be even more devastating than later onset as it may be acquired from an immunosuppressed mother, facilitating the transfer of large numbers of pathogens to a fetus.

For stage B, some conditions have a worse prognosis than others. Galli *et al.* found that anaemia, candidiasis, diarrhoea, cardiomyopathy, hepatitis and persistent fever had a worse prognosis than other events.[6] HIV-associated nephropathy leads to renal failure and death, yet is also in B, while a chronic herpetic ulcer that may respond to acyclovir is in C.

Many conditions seen in Africa are inadequately addressed. Failure to thrive occurs commonly in an African setting and is an independent risk factor for mortality.[3] In the CDC classification, wasting must be accompanied by either chronic diarrhoea or fever for at least 30 days to be classified in C.

Tuberculosis is especially common in HIV-infected children.[7-9] Only disseminated tuberculosis is addressed in the CDC

	TABLE I. DISEASE STAGES IN HIV-INFECTED CHILDREN IN THE USA, 1982 – 1993, PRIOR TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY				
Stage	Time in category (months)	Time to stage C (years)	Percentage reaching stage C in 5 years	Percentage 5-year survival	Median survival (years)
N	10	6.6	50	75	8
A	4	5.7	58	67	7.1
B	65	5.4	60	65	6.8
C	34			17	1.9

classification. A child with multiple episodes of pulmonary tuberculosis may therefore not be adequately classified. Disseminated Bacillus Calmette-Guérin disease is an emerging problem with an extremely poor prognosis yet is also not addressed.[10]

Chronic lung disease, especially bronchiectasis, is seen commonly in children who have not had access to ART, but is not addressed in the CDC system. LIP is classified in B and is considered to have a relatively good prognosis.[11] The differentiation between LIP and bronchiectasis is not easy, and many children with bronchiectasis may be misdiagnosed as having LIP, therefore possibly not receiving ART as they are not considered sick enough. Rectovesical and rectovaginal fistulas are also not addressed but have an extremely poor prognosis.[12]

WORLD HEALTH ORGANIZATION CLASSIFICATION

The World Health Organization (WHO) developed a four-stage classification system for adults in 1994.[13] The staging system has proved useful in Africa and elsewhere.[14-16] A three-stage paediatric classification was introduced in 2002.[17] While superficially easy to use, it did not address many conditions seen in HIV-infected infants. In 2004, after a period of deliberation with paediatricians experienced in treating HIV-infected children, a revised four-stage system was introduced (Table II).[18] It was felt that a four-stage system would be less confusing for health care workers, especially those also dealing with adults, and in addition would assist the transition of children to adulthood when care might be transferred to an adult clinic.

Stage 1 is asymptomatic. Stage 2 includes mainly minor mucocutaneous disorders. Hepatomegaly, hepatospleno-megaly and splenomegaly were placed in stage 2 rather than stage 1 as their presence has been associated with more rapid progression.[19,20] Stages 3 and 4 include conditions seen with progressive disease, stage 4 being more serious and more likely to result in early death. Pulmonary tuberculosis is in stage 3. Despite this, tuberculosis is not an automatic indication for ART; rather, the clinical situation should be evaluated for each child. The WHO recommends ART for both stages 3 and 4. Malnutrition is better addressed, with moderate being a stage 3 and severe a stage 4 event. Bronchiectasis has been included in stage 3 and rectovesical or rectovaginal fistula in stage 4.

Aspects of the classification system still need to be refined. The separation of minor mucocutaneous disorders into a separate stage may be artificial. Wananukul has found increasing frequency of these disorders with increasing disease severity.[21] Areas that need to be addressed include multiple episodes of tuberculosis and whether prognosis worsens with cumulative acquisition of staging criteria.

Malnutrition has been integrated into the classification in a way that is understandable to South African health care workers, with underweight for age allowing classification in stage 3 and marasmus allowing classification in stage 4. Pneumonia occurs commonly and is easily treated with

---

TABLE II. REVISED WHO CLINICAL STAGING OF HIV FOR INFANTS AND CHILDREN*

Stage 1
Asymptomatic
Persistent generalised lymphadenopathy (PGL)
Hepatosplenomegaly

Stage 2
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis)
Papular pruritic eruptions
Seborrhoeic dermatitis
Extensive human papillomavirus infection
Extensive molluscum infection
Herpes zoster
Fungal nail infections
Recurrent oral ulcerations
Lineal gingival erythema (LGE)
Angular cheilitis
Parotid enlargement

Stage 3
Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations
  Unexplained moderate malnutrition[†] not adequately responding to standard therapy (< 3rd centile)
  Unexplained persistent diarrhoea (14 days or more)
  Unexplained persistent fever (intermittent or constant, for longer than 1 month)
  Oral candidiasis (outside neonatal period)
  Oral hairy leukoplakia
  Acute necrotising ulcerative gingivitis/periodontitis
  Pulmonary tuberculosis[‡]
  Severe recurrent presumed bacterial pneumonia
Conditions where confirmatory diagnostic testing is necessary
  Lymphoid interstitial pneumonitis (LIP)
  Unexplained anaemia (< 8 g/dl), neutropenia (< 1 000/mm^3) or thrombocytopenia (< 50 000/mm^3) for more than 1 month
  Chronic HIV-associated lung disease including bronchiectasis

Stage 4
Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations
  Unexplained severe wasting or severe malnutrition[§] not adequately responding to standard therapy (< 60% expected body weight)
  Pneumocystis pneumonia
  Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
  Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration, visceral of any duration)
  Extrapulmonary tuberculosis
  Kaposi's sarcoma
  Oesophageal candidiasis
  CNS toxoplasmosis (outside the neonatal period)
  HIV encephalopathy
Conditions where confirmatory diagnostic testing is necessary
  CMV infection (CMV retinitis or infection of organ other than liver, spleen, or lymph nodes, onset at age 1 month or more)
  Cryptococcal meningitis (or other extrapulmonary disease)
  Any disseminated endemic mycosis (e.g. extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
  Cryptosporidiosis
  Isosporiasis
  Disseminated non-tuberculous mycobacteria infection
  Candida of trachea, bronchi or lungs
  Acquired HIV-related rectal fistula
  Cerebral or B-cell non-Hodgkin's lymphoma
  Progressive multifocal leukoencephalopathy (PML)
  HIV-related cardiomyopathy or HIV-related nephropathy

Stage on ART

*Interim Africa Region Version, for use in those under 15 years with confirmed laboratory evidence of HIV infection; HIV antibody where age >18 months, virological or P24 Ag testing where age < 18 months.
†Moderate malnutrition: Defined as very low weight for age – **http://www.who.int/child-adolescent–health/publications/CHILD_HEALTH/WHO_FCH_CAH_00.1. htm** or **http://www.who.int/nut/documents/manage_severe_malnutrition_eng.pdf**
‡TB is particularly difficult to diagnose in infants and young children.
§Severe malnutrition: Defined as very low weight or visible severe wasting or oedema of both feet – **http://www.who.int/child-adolescent–health/publications/CHILD_HEALTH/WHO_ FCH_CAH_00.1.htm**

TABLE III. PRESUMPTIVE STAGE 4 HIV INFECTION IN INFANTS BELOW 18 MONTHS OF AGE WHERE VIROLOGICAL CONFIRMATION IS NOT POSSIBLE

- HIV seropositive infant less than 18 months symptomatic with 2 or more of following: oral thrush, +/- severe pneumonia, +/- severe wasting/malnutrition, +/- severe sepsis, severe immunosuppression should be suspected and ARV treatment is indicated
- CD4 values where available may be used to guide decision making, CD4% below 25 requires ARV treatment
- Other factors that support diagnosis of clinical stage 4 HIV infection in an HIV-seropositive infant are recent maternal death or advanced HIV disease in mother
- Confirmation of the diagnosis of HIV infection should be sought as soon as possible

antibiotics. For this reason pneumonia has been separated from other causes of bacterial sepsis and is in stage 3. This is of special relevance to children already on ART, in whom intercurrent pneumonia, responding to antibiotics, occurs commonly.

In many parts of Africa, although HIV antibodies can be tested easily in infants below 18 months, virological confirmation is either not possible or takes too long. For these circumstances, the WHO has developed criteria for presumptive stage 4, where ART is indicated (Table III). For the first time this recognises that HIV manifests as a symptom complex rather than just a single staging condition. It also provides justification for starting ART in symptomatic infants without virological confirmation.

A few inconsistencies remain. For example, diarrhoea persisting for > 30 days should be classified in stage 4 regardless of whether a pathogen such as *Cryptosporidium parvum* is identified.

CONCLUSION

The WHO classification has acknowledged conditions commonly seen in Africa and should help with management of children. A revision has been scheduled for 2006. Clinicians working with children have an opportunity for input in improving the classification.

REFERENCES

1. Centers For Disease Control and Prevention. Classification system for human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR Morb Mortal Wkly Rep* 1987; **36:** 225-230.
2. Centers For Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep* 1994; **43:** rr1-12.
3. van Kooten Niekerk NK, Knies MM, Howard J, *et al.* The first 5 years of the family clinic for HIV at Tygerberg Hospital: Family demographics, survival of children and early impact of antiretroviral therapy. *J Trop Pediatr* 2005; 9 June.
4. Barnhart HX, Caldwell MB, Thomas P, *et al.* Natural history of human immunodeficiency virus disease in perinatally infected children: an analysis from the Pediatric Spectrum of Disease Project. *Pediatrics* 1996; **97:** 710-716.
5. Taha TE, Graham SM, Kumwenda NI, *et al.* Morbidity among human immunodeficiency virus-1-infected and -uninfected African children. *Pediatrics* 2000; **106**(6): E77.
6. Galli L, de Martino M, Tovo PA, Gabiano C, Zappa M. Predictive value of the HIV paediatric classification system for the long-term course of perinatally infected children. *Int J Epidemiol* 2000; **29:** 573-578.
7. Schaaf HS, Geldenduys A, Gie RP, Cotton MF. Culture-positive tuberculosis in human immunodeficiency virus type 1-infected children. *Pediatr Infect Dis J* 1998; **17:** 599-604.
8. Jeena PM, Pillay P, Pillay T, Coovadia HM. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. *Int J Tuberc Lung Dis* 2002; **6:** 672-678.
9. Kiwanuka J, Graham SM, Coulter JB, *et al.* Diagnosis of pulmonary tuberculosis in children in an HIV-1 endemic area, Malawi. *Ann Trop Paediatr* 2001; **21:** 5-14.
10. Hesseling AC, Schaaf HS, Hanekom WA, *et al.* Danish bacille Calmette-Guerin vaccine-induced disease in human immunodeficiency virus-infected children. *Clin Infect Dis* 2003; **37:** 1226-1233.
11. Hussey GD, Reijnhart RM, Sebens AM, Burgess J, Schaaf S, Potgieter S. Survival of children in Cape Town known to be vertically infected with HIV-1. *S Afr Med J* 1998; **88:** 554-558.
12. Wiersma R. HIV-positive African children with rectal fistulae. *J Pediatr Surg* 2003; **38(**1): 62-64; discussion 62-64.
13. WHO case definitions for AIDS surveillance in adults and adolescents. *Wkly Epidemiol Rec* 1994; **69**(37): 273-275.
14. Aylward RB, Vlahov D, Munoz A, Rapiti E. Validation of the proposed World Health Organization staging system for disease and infection in a cohort of intravenous drug users. *AIDS* 1994; **8:** 1129-1133.
15. Post FA, Badri M, Wood R, Maartens G. AIDS in Africa – survival according to AIDS-defining illness. *S Afr Med J* 2001; **91:** 583-586.
16. Kassa E, Rinke de Wit TF, Hailu E, *et al.* Evaluation of the World Health Organization staging system for HIV infection and disease in Ethiopia: association between clinical stages and laboratory markers. *AIDS* 1999; **13:** 381-389.
17. World Health Organization. Scaling up antiretroviral therapy in resource limited settings: guidelines for a public health approach. 22-04-02 2002.
18. World Health Organization. Interim WHO Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions For Surveillance African Region. Available at: **whqlibdoc.who.int/hq/2005/WHO_HIV_2005.02.pdf** (accessed 18 September 2005).
19. Tovo PA, de Martino M, Gabiano C, *et al.* Prognostic factors and survival in children with perinatal HIV-1 infection. The Italian Register for HIV Infections in Children. *Lancet* 1992; **339:** 1249-1253.
20. Diaz C, Hanson C, Cooper ER, *et al.* Disease progression in a cohort of infants with vertically acquired HIV infection observed from birth: the Women and Infants Transmission Study (WITS). *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **18:** 221-228.
21. Wananukul S, Thisyakorn U. Mucocutaneous manifestations of HIV infection in 91 children born to HIV-seropositive women. *Pediatr Dermatol* 1999; **16:** 359-363.