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 into account the varying prevalence of pathogens and disease manifestations in different geographical areas.

Classification of HIV disease in children – towards pragmatism?

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

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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

STAGING

CLASSIFICATION OF HIV DISEASE IN CHILDREN – TOWARDS PRAGMATISM?

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KID-CRU and Paediatric Infectious Diseases Unit, Tygerberg Children’s Hospital, Faculty of Health Sciences, Stellenbosch University

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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. It comprised clinical and immunological components, recognising that there could be discordance between the two. Such discordance has been shown in South African children.

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). 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.

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. 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. 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. Only disseminated tuberculosis is addressed in the CDC...
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. Rectovaginal and rectovesical 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, hepatosplenomegaly 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 that 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. Rectovaginal and rectovesical fistulas are also not addressed but have an extremely poor prognosis.12

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1</strong></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Persistent generalised lymphadenopathy (PGL)</td>
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<tr>
<td></td>
<td>Hepatosplenomegaly</td>
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<tr>
<td><strong>Stage 2</strong></td>
<td>Recurrent or chronic upper respiratory tract infections (otitis media, otitis media, sinusitis)</td>
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<tr>
<td></td>
<td>Acute or untreated ulcerative gingivitis/periodontitis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Severe recurrent and symptomatic respiratory infections</td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td>Conditions where confirmatory diagnostic testing is necessary</td>
</tr>
<tr>
<td></td>
<td>Lymphoid interstitial pneumonitis (LIP)</td>
</tr>
<tr>
<td></td>
<td>Unexplained anaemia (&lt; 8 g/dl)</td>
</tr>
<tr>
<td></td>
<td>Severe malnutrition not adequately responding to treatment</td>
</tr>
<tr>
<td></td>
<td>Unexplained moderate malnutrition not adequately responding to standard therapy (&lt; 3rd centile)</td>
</tr>
<tr>
<td><strong>Stage 4</strong></td>
<td>Conditions where confirmatory diagnostic testing is necessary</td>
</tr>
<tr>
<td></td>
<td>Unexplained severe wasting or severe malnutrition not adequately responding to treatment (&lt; 60% expected body weight)</td>
</tr>
<tr>
<td></td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td></td>
<td>Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumococcal)</td>
</tr>
<tr>
<td></td>
<td>Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration, visceral of any duration)</td>
</tr>
<tr>
<td></td>
<td>Extrapulmonary tuberculosis</td>
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<tr>
<td></td>
<td>Kaposi’s sarcoma</td>
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<tr>
<td></td>
<td>Oral candidiasis</td>
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<tr>
<td></td>
<td>CNS toxoplasmosis (outside the neonatal period)</td>
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<tr>
<td></td>
<td>HIV encephalopathy</td>
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</tbody>
</table>

**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, coccidiodymycosis, penicilliosis)
- CNS toxoplasmosis
- 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 leucoencephalopathy (PML)

**Stage on ART**

1. Disseminated non-tuberculous mycobacteria infection
2. Acquired HIV-related rectal fistula
3. Cerebral or B-cell non-Hodgkin’s lymphoma
4. Progressive multifocal leucoencephalopathy (PML)
5. HIV-related cardiomyopathy or HIV-related nephropathy

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*Thrive 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 children weighing less than 80% of standard weight for age. [http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAP_01.1.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAP_01.1.htm)

**Severe malnutrition:** Defined as children weighing less than 70% of standard weight for age. [http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAP_01.1.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAP_01.1.htm)

**Severe malnutrition:** Defined as weighing less than 60% of standard weight for age. [http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAP_01.1.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAP_01.1.htm)

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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.