

## Summary (Last updated November 5, 2018; last reviewed December 15, 2016)

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This report updates the last version of the *Guidelines for the Prevention and Treatment of Opportunistic Infections (OIs) in Children with or Exposed to HIV*, published in 2013.<sup>1</sup> These guidelines are intended for use by clinicians and other health-care workers providing medical care for children living with HIV (CLHIV) and children exposed to but not infected by HIV in the United States. The guidelines discuss opportunistic infections that occur in the United States and ones that might be acquired during international travel, such as malaria. A separate document providing recommendations for prevention and treatment of OIs among adults and post-pubertal adolescents living with HIV (*Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*) was prepared by a panel of adult HIV and infectious disease specialists (see <http://aidsinfo.nih.gov/guidelines>).

HIV-related immunodeficiency is a major risk factor for most of the infections that are discussed in this document, and the prevention or reversal of HIV-related immunodeficiency with antiretroviral therapy (ART) is a key part of prevention and management of OIs in general. Recommendations for ART in children in the United States are developed and regularly updated by a separate panel of pediatric HIV experts (see [Ped ARV Guidelines](#)). In the United States, it has become standard practice for all children with HIV infection to be treated with ART (see [What to Start](#) in the [Ped ARV Guidelines](#)). Therefore, the Panel has framed its OI prevention and treatment recommendations on the expectation that children are already receiving or preparing to start ART.

These guidelines are developed by a panel of specialists in pediatric HIV infection and infectious diseases (the [Panel on Opportunistic Infections in Children with or Exposed to HIV](#)) from the U.S. government and academic institutions. For each OI, one or more pediatric specialists with subject-matter expertise reviews the literature for new information since the last guidelines were published, and then proposes revised recommendations for review by the full Panel. After these reviews and discussions, the guidelines undergo further revision, with review and approval by the Panel, and final review and endorsement by the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Disease Society (PIDS). The Panel also received input from the American Academy of Pediatrics (AAP).

After the 2013 full guidelines release, the Panel modified its process so that individual sections would be published as they were updated, allowing for more timely appearance of new recommendations. Each section will be marked with the date of its last update. The Panel's goal is to review each section for updates approximately every 2 years, with shorter intervals in response to availability of new treatments or relevant research findings.

So that readers can ascertain how best to apply the recommendations in their practice environments, each recommendation is rated for the strength of the recommendation and the quality of the evidence supporting that recommendation. After the 2013 guidelines release, the evidence review and recommendation rating system underwent major changes and this new approach is incorporated into sections as they are individually updated. As a result, topics not yet updated since the 2013 release reflect the former rating system, and sections updated since 2013 use a newer, modified GRADE system. A description of the methods of collecting and synthesizing evidence and formulating and rating recommendations appears in the [Background and Recommendations Rating Scheme](#) section.

Other guideline considerations appearing in Appendix 1 (Important Guidelines Considerations) include a description of the make-up and organizational structure of the Panel, definition and management of conflicts of interest, funding sources for the guidelines, public commentary, and plans for updating the guidelines. The names and financial disclosures for each of the Panel members are listed in Appendices 2 and 3, respectively.

An important mode of childhood acquisition of OIs and HIV infection is from infected mothers. Women living with HIV (WLHIV) may be more likely to have coinfections with opportunistic pathogens (e.g.,

hepatitis C), and more likely than women who are not HIV-infected to transmit these infections to their infants. In addition, women or other family members living with HIV coinfecting with certain opportunistic pathogens, may be more likely to transmit these infections horizontally to their children, resulting in increased likelihood of primary acquisition of such infections in young children. Furthermore, transplacental transfer of antibodies that protect infants against serious infections may be lower in WLHIV than in women who are HIV-uninfected. Therefore, infections with opportunistic pathogens may affect not just infants living with HIV but also infants who were exposed to but not infected by HIV. These guidelines for treating OIs in children, therefore, consider treatment of infections in all children—those living with HIV and those who do not have HIV—born to WLHIV.

In addition, HIV infection is increasingly common in adolescents who are long-time survivors of perinatal infection, or who acquired HIV infection as teens. Guidelines for post-pubertal adolescents can be found in the adult OI guidelines, but drug pharmacokinetics (PK) and response to treatment may differ in younger adolescents who are prepubertal or in an early stage of puberty. Therefore, these guidelines also apply to treatment of youth living with HIV who have not yet completed pubertal development.

The most important recommendations are highlighted in boxed major recommendations preceding each section, and a table of dosing recommendations appears at the end of each section. The guidelines conclude with summary tables that display dosing recommendations for all of the conditions, drug toxicities, and drug interactions, and figures summarizing immunization recommendations.

CD4+ T-lymphocyte (CD4) cell count and CD4 percentage are well-established measures of immune status in HIV infection. HIV disease stage—and risk of OI—is categorized based on age-specific CD4 counts and CD4 percentages.<sup>2</sup> Note that CD4 thresholds for young children ( $\leq 5$  years old) are different from those for older children ( $\geq 6$  years old), adolescents and adults (see Table 1). Historically, CD4 percentage was more commonly used in studies of children with HIV infection because CD4 percentages have less age-related variation while CD4 counts normally decline with increasing age; furthermore, studies which characterized OI risk, and evaluated prevention and treatment interventions, were not consistent in the CD4 values they used. As a result, the evidence supporting OI recommendations is presented according to the CD4 values used in the relevant studies, but, in many cases, the recommendations will be adjusted to reflect the current thresholds for CD4-defined HIV disease stage.<sup>2</sup> In addition, if the recommendation is expressed in terms of CD4 count, then a footnote may be used to indicate the corresponding CD4 percentages, and vice-versa.

**Table 1: HIV infection stage\* based on age-specific CD4+ T-lymphocyte (CD4) count or CD4 percentage of total lymphocytes**

Stage	Age on date of CD4 test					
	<1 year		1-5 years		$\geq 6$ years	
	Cells/uL	%	Cells/uL	%	Cells/uL	%
1	$\geq 1,500$	$\geq 34\%$	$\geq 1,000$	$\geq 30$	$\geq 500$	$\geq 26$
2	750-1499	26-33	500-999	22-29	200-499	14-25
3	$< 750$	$< 26$	$< 500$	$< 22$	$< 200$	$< 14$

\* The stage is based primarily on the CD4 count; the CD4 count takes precedence over the CD4 percentage, and the percentage is considered only if the count is missing. If a stage-3-defining opportunistic illness has been diagnosed (see [MMWR 2014 Appendix](#)), then the stage is 3 regardless of CD4 test results.

Modified from: Centers for Disease Control and Prevention: 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age MMWR 1994;43(No. RR-12); and Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. MMWR 2014;63(No. RR-3):1-10.

The terminology for describing use of antiretroviral (ARV) drugs for treatment of HIV infection has been standardized to ensure consistency within the sections of these guidelines. Combination antiretroviral therapy (cART) and its older synonym, highly active antiretroviral therapy (HAART), historically refer to the use of

multiple (generally 3 or more) ARV drugs from different classes as part of an HIV treatment regimen that is designed to achieve virologic suppression. The term ART has been used when referring to use of ARV drugs for HIV treatment more generally, including cART and (mostly historical) use of 1- or 2-agent ARV regimens that do not meet criteria for cART. In these guidelines, we will use ART as the preferred term and only use cART or HAART when necessary for historical purposes.

Because treatment of OIs is an evolving science, and availability of new agents or clinical data on existing agents may change therapeutic options and preferences, these recommendations will be periodically updated and will be available at <http://AIDSinfo.nih.gov>.

## References

1. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections (OIs) in HIV-Exposed and HIV-Infected Children. 2013. Available at <https://aidsinfo.nih.gov/guidelines/archive/pediatric-oi-guidelines>.
2. Centers for Disease C, Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR* Recomm Rep. 2014;63(RR-03):1-10. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24717910>.