Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children (Last updated November 1, 2012; last reviewed November 1, 2012)

General Considerations

Panel's Recommendations
• Combination therapy consisting of a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone with either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor is recommended for initial treatment of HIV-infected children **(AI)**. • The goal of therapy in treatment-naive children is to reduce plasma HIV RNA levels to below the limits of quantitation using the most sensitive assays and to preserve or normalize immune status **(AI)**. • Antiretroviral (ARV) drugs initiated for chemoprophylaxis of maternal-child transmission of HIV should be discontinued in infants who are confirmed to be HIV-infected **(AI)**. • ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive infants, children, and adolescents (**AII** infants; **AIII** children and adolescents).
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion* *† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents*

More than 20 antiretroviral (ARV) drugs are Food and Drug Administration-approved for use in HIV-infected adults and adolescents and 19 have an approved pediatric treatment indication.[1] The majority of the agents approved for use in pediatric patients are available as a liquid, powder, chewable tablet, or small capsule or tablet suitable for pediatric use. ARV drugs fall into several major drug classes: nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. Information on drug formulation, pediatric dosing, and toxicity for the individual drugs and detailed information on drug interactions can be found in Appendix A: Pediatric Antiretroviral Drug Information. Over time, new drugs and drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles will likely become available, which will increase treatment options for children.

Combination antiretroviral therapy (cART) with at least three drugs from at least two drug classes is recommended for initial treatment of HIV-infected infants, children, and adolescents because it provides the best opportunity to preserve immune function and delay disease progression.[2-5] The goal of cART is to maximally suppress viral replication, preferably to below the limits of quantification, for as long as possible while preserving and/or restoring immune function and minimizing drug toxicity. Combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic

response, and delays development of viral mutations that confer resistance to the drugs being used.[4-6]

If an infant is confirmed to be HIV-infected while receiving chemoprophylaxis to prevent mother-to-child transmission (PMTCT) of HIV, prophylactic ARV drugs should be discontinued promptly and treatment initiated with a combination regimen of at least three drugs. Zidovudine can be included as a component of the treatment regimen if zidovudine drug resistance is not detected.

Treatment-naive infants and children with perinatal HIV infection can have drug-resistant virus either because it was transmitted perinatally or during breastfeeding or because resistance developed while they were receiving ARV prophylaxis. Thus, ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive infants and children. In infants receiving prophylactic ARV drugs for PMTCT, ARV drug resistance testing can be performed at the same time as confirmatory HIV testing or when prophylactic ARV drugs are discontinued. In a study in New York State, genotypic drug resistance was identified in 12% of 91 HIV-infected infants born from 1998 to 1999 and in 19% of 42 infants born from 2000 to 2001.[7, 8] Detection of resistance in the infants was not significantly associated with a history of maternal and infant ARV prophylaxis. Similarly, following initiation of treatment, mutations associated with drug-resistance were detected in 24% of 21 infants at a median age of 9.7 weeks. Most of the mutations were not associated with maternal/infant prophylaxis regimens and resistant virus was persistently archived in the resting CD4 cell reservoir in all the infants. In a study in Africa, infants, regardless of whether they were exposed to nevirapine as part of PMTCT, had higher rates of virologic failure on nevirapine-based regimens compared with lopinavir/ritonavir-based regimens.[9-11] In a Spanish cohort of children, resistance mutations were detected in 13% of treatment-naive children.[12] In the United States and Europe, drug-resistant virus has been identified in 6% to 16% of ARV-naive adults and 18% of adolescents with recently acquired HIV infection.[13-17] For ARV-naive children beyond infancy, limited available data do not demonstrate that resistance testing before initiation of therapy correlates with greater success of initial ART.[18] Nevertheless, because the prevalence of resistance in HIV-infected children is sufficiently high and on the basis of expert opinion, the Panel recommends ARV drug-resistance testing with a genotypic assay before initiation of therapy in all treatment-naive infants and children and use of resistance testing results to select the initial drug combination.[19] (See Antiretroviral Drug-Resistance Testing.) Resistance testing in HIV-infected adolescents and adults is also recommended at entry into care.

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