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Personalized Therapeutics: HIV Treatment in Adolescents

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Abstract

Adolescents infected with human immunodeficiency virus (HIV) represent a heterogeneous group of pubertal children and young adults. Antiretroviral therapy (ART) in adolescents is complex and depends on multiple factors. The continued use of higher (weight- or surface-based) pediatric doses can result in potentially toxic drug exposure, whereas early introduction of lower adult doses can lead to the development of drug resistance and virologic failure. The physiological and psychosocial changes during puberty create strong grounds for an individualized therapeutic approach in HIV-infected adolescents.

Despite significant progress in the prevention of mother-to-child transmission of human immunodeficiency virus (HIV) infection, it was estimated that there were 2.3 million children under the age of 15 years with HIV infection in 2006.1 Among those, ~780,000 (600,000–1,000,000) were estimated to be in need of antiretroviral therapy (ART). In the United States and other developed countries, an increasing number of children with perinatally acquired HIV infection are now surviving into adolescence and adulthood. In addition, large numbers of American teenagers continue to acquire HIV infection through sexual contact and intravenous drug use; youths between 13 and 24 years of age account for 15% of the 40,000 new HIV cases per year.2 Based on the strengthening global response to the problem of HIV/AIDS in recent years, the number of adolescents receiving ART worldwide is rapidly increasing.3 Given the growing number of HIV-infected youth with access to ART, a better understanding of the disposition of antiretroviral (ARV) drugs during puberty is urgently needed. The selection of ART dosages for patients in the pubertal stages of maximal growth is left to the provider's discretion, and individual differences in the progression to sexual maturation are often not provided for. The recently published report by the Committee on Pediatric AIDS, dealing with increasing access to antiretroviral

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CONFLICT OF INTEREST

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(ARV) drugs for pediatric patients, identifies the lack of appropriate dosing of ARV drugs in adolescents as one of the barriers to providing ART to HIV-infected children and youth globally.3 The report underlines that, even with the availability of appropriate ART, the pharmacokinetic (PK) data may be insufficient to appropriately guide the dosing in adolescent patients, who may need higher than "maximum adult dose" to ensure adequate drug exposure.3,4 Consequently, adolescents are identified as a separate study cohort when investigating the PK and pharmacodynamics (PD) of ARV agents in children, and the need for phase II and III studies in this cohort is underscored.

Several pediatric HIV research networks (Pediatric AIDS Clinical Trials Group (PACTG)/ HIV Prevention Trials Network/International Maternal Pediatric Adolescent AIDS Clinical Trials, Collaborative HIV Pediatric Study, Pediatric European Network for Treatment of AIDS, the HIV Netherlands Australia Thailand Research Collaboration, and Adolescent Medicine Trials Network) have addressed issues of developmental PK/PD of ART in HIV-infected pediatric patients. However, very few studies have investigated the PK/PD of ARV agents in adolescents and young adults. The PK of abacavir were reported from the PACTG protocols P1018 and P1052;5,6 lamivudine and zidovudine data (including data on phosphorylation to the intracellular triphosphate metabolites) were collected in PACTG studies P1012 and P1052;7 lopinavir/ritonavir and saquinavir were studied in PACTG protocol P1038;8 and atazanavir was studied in PACTG protocol 1020A and in Adolescent Medicine Trials Network studies along with tenofovir.5,9 The PACTG protocol P1038 and the author's study in children with experience of ARV suggested that the use of high doses of lopinavir/ritonavir might be required for salvage HIV therapy in adolescent patients.8,10 The Adolescent Medicine Trials Network study by Kiser *et al.* evaluated the PK of the combined administration of atazanavir/ritonavir and tenofovir in young adults with HIV infection.9 A higher level of tenofovir exposure was expected on the basis of data from healthy volunteers, but this was not seen in HIV-infected subjects, most likely because of a faster tenofovir clearance, as apparent in the higher creatinine clearances observed in this age group.9 None of the available studies in adolescents has investigated the effects of pubertal changes on the required dosage in ART, and information on failed ART or increased drug resistance in HIV-infected adolescents is very limited. No studies have addressed the important issue of the long-term effects of ART exposure during puberty. Such possible effects include ART-associated hyperlipidemia and a risk of developing cardiovascular disease. Finally, adolescent patients are frequently exposed to antidepressants, hormonal contraceptives, anabolic steroids, alcohol, and illicit drugs. No studies are available to date on the effects of psychotropic drugs, substance abuse, and exogenous sex hormones on ART drug disposition and efficacy in adolescence, although there is an abundance of pharmacological data pertaining to the adult population.

HIV-infected adolescents represent a heterogeneous group of pubertal children and young adults at different stages of psychosocial development, with vertically and horizontally transmitted HIV infection, varying demographic and socioeconomic statuses, and diverse histories of sexual and substance abuse. The choice of ART regimen must balance many of these factors in addition to the selection of the correct dosage of ARV drugs. Clinicians are faced with the dilemma of choosing a dosing regimen that falls somewhere between pediatric (weight- and surface-based) and adult (fixed-dose) guidelines. The World Health Organization guidelines and the US guidelines for ART in adolescent patients include adolescents within both categories: "pediatric" (infants and children) and "adults and adolescents." The World Health Organization defines the "adolescent" cohort as children aged between 10 and 19 years; the US guidelines use 12 years of age as the cutoff for transition to adolescence.5,11 (Table 1) The appropriate dosing of ARV medications in adolescents is complex and depends on multiple factors, including developmental changes throughout puberty. Although current pediatric HIV treatment guidelines for older children

recommend considering Tanner stages of puberty when prescribing ART, they do not provide data justifying those recommendations. For children in early puberty (Tanner stages I and II), the US guidelines recommended using pediatric schedules, whereas for adolescents in their growth spurt (Tanner stages III and IV), both adult and pediatric dosing schedules are recommended.5 The World Health Organization pediatric guidelines extend pediatric dosing to Tanner stage III and recommend adult dosing in adolescents in Tanner stages IV and V.11 Both guidelines recommend considering issues such as toxicity, adherence, and virologic and immunologic parameters when determining the timing of transition from pediatric to adult doses. The continued use of higher (weight- or surface-based) pediatric doses during adolescence can result in increased and potentially toxic drug exposure, whereas early introduction of lower adult doses can lead to suboptimal therapeutic exposure and development of drug resistance and subsequent virologic failure.

Few studies have addressed the effect of HIV infection and ART on puberty, and these were conducted in adolescents with perinatally acquired HIV infection in the era of limited therapeutic choices.12,13 The study by De Martino *et al.* reported a delay in the onset of puberty in Caucasian HIV-infected children independent of clinical or immunological status. 12 A much larger prospective cohort study from the United States, carried out by the PACTG 219 Study Team among children of diverse ethnic and racial backgrounds, reported a direct association between immunosuppression and a delayed onset of puberty.13 This study, however, simplified the classification of Tanner stages and did not record orchidometric data. This omission could lead to a potential misclassification of the Tanner stage. Recently, a much smaller longitudinal study of 10 HIV-infected children, involving a thorough puberty evaluation including serial quantitations of plasma growth hormones (GHs), gonadotropins, and sex steroids, has demonstrated that children with a good control of HIV infection showed growth and pubertal development within the physiological percentile for their age.14 Further studies are necessary to understand the impact of perinatally and behaviorally acquired HIV infection and ART on the onset and progression of puberty.

Puberty is characterized by an increase in growth velocity, changes in body composition, and the appearance of striking somatic changes. The changes in body composition vary between the sexes, with a significant increase in lean body mass in boys and an accumulation of fat in girls.15,16 Girls are generally a year or two more advanced in pubertal maturation than boys, and the African-American race has been associated with an earlier onset of menarche.16,17 Peak height velocity in girls occurs before menarche (which in turn takes place ~2–2.5 years after the first signs of breast development), whereas significant changes in genital development usually precede peak height velocity in boys.18 In each gender, it takes about 4.5 years (3–6 years) from the first appearance of secondary sex characteristics to adult body configuration. Significant hormonal changes occur during adrenarche just prior to the appearance of secondary sexual characteristics, and gonadotropins, sex steroids, and GHs show different secretory patterns during different pubertal stages in boys and girls. The increase in circulating GH and insulin-like GH (IGF-1) levels is seen in girls at Tanner stage II (Breast II), whereas in boys it is usually delayed until stages II to III (Genital II–III).19 In boys, rapidly rising testosterone levels cause an increase in GH/IGF-1 secretion and growth velocity. In girls, mean plasma levels of estradiol have been shown to rise steadily throughout puberty, with wide individual fluctuations depending on the time relative to menarche and the ovulatory cycle.19 A careful history and thorough physical examination by an experienced provider is required for accurately evaluating the onset and progress of puberty.

To date, little attention has been paid to the developmental processes of puberty, and drug PK/PD data in the adolescent population are remarkably limited.20 The concept of

adolescent developmental pharmacology was proposed by Hein in 1987.21 Since then, few PK studies have been published in this field.22–24 Changes in the effects of ABCB1 polymorphisms on the bioavailability of oral cyclosporine have been shown to occur in pediatric renal transplant patients >8 years of age as compared to younger children.24 The sexual maturation rate was shown to affect the net renal tubular secretion of digoxin.25 Tanner stage and presence of sex steroids were shown to affect the clearance of antipyrine.22 Puberty has also been shown to affect the activity of selected CYP450 isoforms. Using a caffeine breath test, Lambert *et al.* demonstrated an association between Tanner stage and age-dependent inducibility of the CYP1A2 pathway.23 The correlation with Tanner stage appeared to be sex-dependent, with a decrease in clearance seen at an earlier Tanner stage in girls than in boys. Similar data on sex-associated differences were observed in studies on theophylline metabolism in adolescents.26 A recent study by Saitoh *et al.* on the effect of CYP2B6 on efavirenz PK in HIV-infected children has demonstrated that age and CYP2B6 G516T genotype were independently and statistically associated with efavirenz clearance.27 These results suggest that age-related changes in CYP2B6 activity may need to be considered when evaluating the impact of genetic variants on efavirenz PK in children. Developmental changes in CYP450 activity have the potential to affect disposition and clearance of non-nucleoside reverse transcriptase inhibitors and protease inhibitors during puberty and may produce new models of drug–drug interactions with CYP450 substrates, inducers, and suppressors such as those used in concomitant ARV and antimycobacterial therapy.

A high level of patient adherence to the regimen is required to achieve a successful outcome for ART.28 It must be recognized that HIV-infected adolescents face multiple challenges in fulfilling the adherence requirements because of the dynamic period of transition from childhood to adulthood. In addition to the well-recognized pediatric adherence barriers such as dependence on a caregiver for obtaining medications, palatability, pill burden, and interference with lifestyle, many obstacles to adherence emerge in adolescence, and these are related to the psychosocial changes during puberty. Among these are changes in lifestyle involving growing independence and rebellion against parental involvement, increased peer pressure and fear of stigmatization, increased risk-taking behavior, denial and fear of HIV infection (particularly in recently diagnosed youth), long history of poor adherence and nondisclosure issues in perinatally infected adolescents, psychiatric problems (depression), and alcohol and substance abuse.29,30 A comprehensive assessment of adherence through multiple methods (such as self-report, pill count, pharmacy refills, and therapeutic drug monitoring) should be incorporated into the ART of every adolescent HIV patient. Although strategies to promote long-term adherence to ART have not been rigorously evaluated in adolescents to date, preliminary data suggest that interventions based on intensive follow-up, involvement of family and peers, use of reminder systems, alternative dosing schedules, and directly observed therapy may facilitate adherence to the dosing regimen in this vulnerable population.30

The developmental physiological, psychological, and social changes during puberty create strong grounds for an individualized therapeutic approach to HIV-infected adolescents. The concept of developmental rather than chronological age needs to be considered in adolescents. As the use of ART continues to expand among an aging cohort of HIV-infected children and newly infected adolescents, large collaborative studies are urgently needed to evaluate ARV drug exposure in adolescents, and accurate growth curves and sexual maturation staging of HIV-infected children and adolescents of various ethnic and racial backgrounds need to be developed. Finally, better adherence interventions and simplified ART regimens with newer ARV agents are needed to improve the outcome of therapy in HIV-infected adolescents.

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References

1. UNAIDS. AIDS epidemic update: December 2007. 2008 [Accessed 11 June 2008]. <http://data.unaids.org/pub/EPISlides/2007/2007_epiupdate_en.pdf>
2. CDC. HIV/AIDS Surveillance Report. 2006. Atlanta: US Department of Health and Human Services; 2008.
3. Havens PL, Gibb DM. American Academy of Pediatrics Committee on Pediatric AIDS, Section on International Child Health. Increasing antiretroviral drug access for children with HIV infection. Pediatrics. 2007; 119:838–845. [PubMed: 17403860]
4. Grub S, et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. Clin. Pharmacol. Ther. 2002; 71:122–130. [PubMed: 11907486]
5. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2008 [Accessed 27 June 2008]. <http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf>
6. Rodman, JH., et al. Abacavir systemic clearance in children is highly influenced by glucuronidation phenotype. 14th International AIDS Conference; 5–12 July 2002; Barcelona, Spain. Abstract MoPpB2010.
7. Flynn PM, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. Antimicrob. Agents Chemother. 2007; 51:3516–3522. [PubMed: 17664328]
8. Robbins BL, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in HIV infected pediatric and adolescent patients previously treated with protease inhibitors. Antimicrob. Agents Chemother. 2008; 52:3276–3283. [PubMed: 18625762]
9. Kiser JJ, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. Antimicrob. Agents Chemother. 2008; 52:631–637. [PubMed: 18025112]
10. Rakhmanina, N., et al. Recommended dose of lopinavir/ritonavir is suboptimal in protease inhibitor-experienced children. 15th Conference on Retroviruses and Opportunistic Infections; 3–6 February 2008; Boston, MA. Abstract 574.
11. WHO. Antiretroviral therapy for HIV infection in infants and children: towards universal access. 2006 [Accessed 23 June 2008]. <http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf>
12. de Martino M, et al. Puberty in perinatal HIV-1 infection: a multicentre longitudinal study of 212 children. AIDS. 2001; 15:1527–1534. [PubMed: 11504985]
13. Buchacz K, et al. Delayed onset of pubertal development in children and adolescents with perinatally acquired HIV infection. J. Acquir. Immune Defic. Syndr. 2003; 33:56–65. [PubMed: 12792356]
14. Titone L, et al. Hormonal, auxological and clinical follow-up in children with connatal HIV infection. Personal records. Minerva Pediatr. 2006; 58:461–467. [PubMed: 17008857]
15. Kreipe, R. Normal somatic adolescent growth and development. In: McAnarney, ER., et al., editors. Textbook of Adolescent Medicine. Vol. 57. Philadelphia, PA: WB Saunders; 1992.
16. Tanner, J. Growth at Adolescence. London, England: Blackwell Scientific; 1962.
17. National Center for Health Statistics: Age at menarche, US. 1973; 133(11):2–3.
18. Abbassi V. Growth and normal puberty. Pediatrics. 1998; 102(2 Pt 3):507–511. [PubMed: 9685454]

19. Albertsson-Wikland K, Rosberg S, Karlberg J, Groth T. Analysis of 24-hour growth hormone profiles in healthy boys and girls of normal stature: relation to puberty. J. Clin. Endocrinol. Metab. 1994; 78:1195–1201. [PubMed: 8175978]
20. Rogers A. A. Pharmacokinetics and pharmacodynamics in adolescents. January 20–21, 1994. Proceedings. J. Adolesc. Health. 1994; 15:605–678. [PubMed: 7696278]
21. Hein K. Developmental pharmacology in adolescence. The inauguration of a new field. J. Adolesc. Health Care. 1987; 8:1–4. [PubMed: 3818402]
22. Linday LA, et al. Changes in salivary antipyrine pharmacokinetics during adolescence, correlated with age, hormonal levels and Tanner stage. Dev. Pharmacol. Ther. 1991; 16:194–202. [PubMed: 1782837]
23. Lambert GH, Schoeller DA, Kotake AN, Flores C, Hay D. The effect of age, gender, and sexual maturation on the caffeine breath test. Dev. Pharmacol. Ther. 1986; 9:375–388. [PubMed: 3102191]
24. Fanta S, et al. Pharmacogenetics of cyclosporine in children suggests an age-dependent influence of ABCB1 polymorphisms. Pharmacogenet. Genomics. 2008; 18:77–90. [PubMed: 18192894]
25. Linday LA, Drayer DE, Khan MA, Cicalese C, Reidenberg MM. Pubertal changes in net renal tubular secretion of digoxin. Clin. Pharmacol. Ther. 1984; 35:438–446. [PubMed: 6368090]
26. Cary J, Hein K, Dell R. Theophylline disposition in adolescents with asthma. Ther. Drug Monit. 1991; 13:309–313. [PubMed: 1780962]
27. Saitoh A, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. J. Acquir. Immune Defic. Syndr. 2007; 45:280–285. [PubMed: 17356468]
28. Williams PL, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics. 2006; 118:e1745–e1757. [PubMed: 17101712]
29. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Adolescent Medicine HIV/AIDS Research Network. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. AIDS Care. 2001; 13:27–40. [PubMed: 11177463]
30. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. Pediatrics. 2007; 119:e1371–e1383. [PubMed: 17533177]

Table 1

Recommended doses of antiretroviral medications in adolescent[a] patients according to WHO and US guidelines[b]

Drug	WHO guidelines	US guidelines
Abacavir (ABC, Ziagen®)	Children <16 years or body weight <37.5 kg—8 mg/kg/dose twice daily. Maximal dose—>16 years or ≥37.5 kg—300 mg/dose twice daily. Once daily dosing is not yet approved in children but encouraging PK data is available. Adults—300 mg/dose twice daily or 600 mg once daily. Combination ART: • 300 mg AZT/150 mg 3TC/300 mg ABC—1/dose twice daily.	Pediatric[c] 8 mg/kg/dose (maximal dose, 300 mg) twice daily. Adolescent: There is limited ABC data for adolescents. Adolescent >16 years/adults: 300 mg/dose twice daily or 600 mg/dose once daily. Combination ART (adults): • Trizivir® (300 mg AZT/150 mg 3TC/300 mg ABC)—1 tablet/dose twice daily. • Epzicom™ (300 mg 3TC/600 mg ABC)—1 tablet/dose once daily.
Didanosine (dideoxinosine, ddI, Videx®)	Children <13 years of age—90–120 mg/m^2/dose twice daily. Maximal dose—>16 years or body weight >60 kg—200 mg/dose twice daily or 400 mg/dose once daily (enteric coated (EC)). Once daily dosing for chewable tablets is authorized in the United Kingdom for children >6 years of age. Adults—body weight >60 kg—400 mg once daily, body weight <60 kg—250 mg once daily.	Pediatric: 90–150 mg/m^2/dose twice daily (average dose 120 mg/m^2) or in *treatment-naive* patients 3–21 years of age 240 mg/m^2/dose once daily. Adolescent/adults: oral solution—body weight >60 kg—200 mg/dose twice daily or 250 mg/dose, if co-administered with TDF. Body weight <60 kg—125 mg/dose twice daily. The total daily dose may be administered once daily, twice daily dosing is preferred.
Emtricitabine (FTC, Emtriva™)	No dosing guidelines for children. Adults—200 mg/dose once daily.	Pediatric: oral solution—6 mg/kg/dose (maximal dose, 240 mg) once daily. Capsules (body weight >33 kg)—200 mg/dose once daily. Adolescent >18 years/adults: oral solution—240 mg/dose once daily, capsules—200 mg/dose once daily. Combination ART (adults): • Truvada® (200 mg FTC/300 mg TDF)—1 tablet/dose once daily. • Atripla™ (200 mg FTC/300 mg TDF/600 mg EFV)—1 tablet/dose once daily.
Lamivudine (3TC, Epivir®, Epivir HBV)	Body weight <50 kg—4 mg/kg/dose twice a day to a maximum of 150 mg/dose twice daily. Body weight >50 kg—150 mg/dose twice daily. Adults—150 mg/dose twice daily or 300 mg once daily. Combination ART: • 300 mg AZT/150 mg 3TC—1 tablet/dose twice daily. • 300 mg AZT/150 mg 3TC/300 mg ABC—1 tablet/dose twice daily. • 30 mg d4T/150 mg 3TC/200 mg NVP—1 tablet/dose twice daily.	Pediatric: 4 mg/kg/dose (maximal dose, 150 mg) twice daily. Adolescent ≥16 years/adults: body weight >50 kg—150 mg/dose twice daily or 300 mg/dose once daily. Body weight <50 kg—4 mg/kg/dose (maximal dose, 150 mg) twice daily. Combination ART (adolescents >12 years/adults): • Combivir® (300 mg AZT/150 mg 3TC)—1 tablet/dose twice daily. • Trizivir® (300 mg AZT/150 mg 3TC/300 mg ABC)—1 tablet/dose twice daily. • Epzicom® (300 mg 3TC/600 mg ABC)—1 tablet/dose once daily.

Drug	WHO guidelines	US guidelines
Stavudine (d4T, Zerit®)	Body weight <30 kg—1 mg/kg twice daily. Body weight >30 kg—30 mg/dose twice daily. Body weight >60 kg—40 mg/dose twice daily (using 30 mg dosing leads to delay or reduction of toxicity, although limited data on efficacy is available). Adults—body weight >60 kg—40 mg/dose twice daily, body weight <60 kg—30 mg/dose twice daily. Combination ART: • 1 mg/kg/dose d4T plus 4 mg/kg/dose 3TC (oral solution) twice daily or 30 mg d4T/150 mg 3TC (1 tablet/dose) twice daily. • 30 mg d4T/150 mg 3TC/200 mg NVP—1 tablet/dose twice daily.	Pediatric: body weight <30 kg—1 mg/kg/dose twice daily. Adolescent (body weight ≥30 kg)/adults: body weight 30–<60 kg—30 mg/dose twice a day. Body weight ≥60 kg—40 mg/dose twice daily.
Tenofovir (TDF, Viread®)	No dosing guidelines for children. Adults—300 mg once daily.	Pediatric: investigational dose—210 mg/m^2/dose (maximal dose, 300 mg) once daily. Adolescent >18 years/adults: 300 mg/dose once daily. Combination ART (adults): • Truvada® (200 mg FTC/300 mg TDF)—1 tablet/dose once daily. • Atripla™ (200 mg FTC/300 mg TDF/600 mg EFV)—1 tablet/dose once daily.
Zidovudine (ZDV, AZT, Retrovir®)	Children—180–240 mg/m^2/dose (maximal dose, 300 mg) twice daily. Adults—250–300 mg/dose twice daily. Combination ART: • 300 mg AZT/150 mg 3TC—1 tablet/dose twice daily. • 300 mg AZT/150 mg 3TC/300 mg ABC (tablet)—1 tablet/dose twice daily.	Pediatric: 160 mg/m^2/dose every 8 hours (three times daily) or 180–240 mg/m^2/dose twice daily. Adolescent ≥12 years/adults: 200 mg/dose three times daily or 300 mg/dose twice daily. Combination ART (adolescent/adults): • Combivir® (300 mg AZT/150 mg 3TC)—1 tablet/dose once daily. • Trizivir® (300 mg AZT/150 mg 3TC/300 mg ABC)—1 tablet/dose once daily.
Efavirenz (DMP-266EFV, Sustiva™)	Body weight <40 kg—19.5 mg/kg/day (syrup) or 15 mg/kg/day (capsule/tablet). Body weight >40 kg—600 mg/dose once daily.	Pediatric: body weight <40 kg (20–<25 kg—300 mg; 25–<32.5 kg—350 mg; 32.5–<40 kg—400 mg) once daily. Adolescent (body weight ≥40 kg)/adults: 600 mg/dose once daily. Combination ART (adults): • Atripla™ (200 mg FTC/300 mg TDF/600 mg EFV)—1 tablet/dose once daily. • Co-administration with certain PIs requires following dose adjustments—300 mg ATV plus 100 mg RTV with 600 mg EFV, all once daily; 1,000 mg IDV 3 times daily plus 600 mg EFV once daily; 700 mg f-AMP plus 100 mg RTV once daily or 1,400 mg f-APV plus 300 mg RTV with 600 mg EFV, all once daily. • Co-administration with MVC requires 600 mg MVC twice daily with 600 mg EFV once daily. Combination ART (adolescents >12 years/adults):

Drug	WHO guidelines	US guidelines
	Adults—600 mg/dose once daily.	• Co-administration with LPV/RTV requires 600 mg LPV/150 mg RTV (3 tablets) twice daily with 600 mg EFV once daily.
Etravirine (ETR, Intelence™, ™C125)	No dosing guidelines for children. No dosing guidelines for adults.	Pediatric: not approved for use in children. Adolescent/adults: adult dose for ARV-experienced patients 200 mg/dose twice daily.
Nevirapine (NVP, Viramune®)	Children: 160–200 mg/m^2/dose (maximal dose, 200 mg) twice daily. Scale up the dosing schedule at initiation starting at 160 mg/m^2 once daily for the first 14 days, and moving up to full dose if no rash or untoward effects after 14 days. Adults—200 mg/dose once daily for 14 days, followed by 200 mg/dose twice daily. Combination ART: 30 mg d4T/150 mg 3TC/200 mg NVP—1 tablet/dose twice daily.	Pediatric: 150–200 mg/m^2/dose (maximal dose, 200 mg) twice daily. Scale up the dosing schedule at initiation starting at 150 mg/m^2/dose once daily for the first 14 days, and moving up to full dose if no rash or untoward effects after 14 days. Adolescent/adults: 200 mg/dose twice daily. Combination ART (adolescents >12 years/adults): • Co-administration with LPV/RTV requires dose adjustment for LPV/RTV. Combination ART (adults): • Co-administration with MVC requires 150 mg MVC dose with 200 mg NVP, all twice daily.
Atazanavir (ATV, Reyataz™)	No dosing guidelines for children. Adults—300 mg ATV plus 100 mg RTV once daily.	Pediatric: Not approved for use in children. Currently under the study in PACTG/ IMPAACT 1020 A. Adolescent ≥16–21 years/adults: in treatment-naive patients—400 mg daily (this dose may be inadequate). In treatment-experienced patients—300 mg plus 100 mg RTV once daily. Combination ART (adults): • Only RTV-boosted ATV (300 mg ATV plus 100 mg RTV) should be used in combination with TDF, LPV/RTV. • Co-administration with MVC requires 150 mg MVC dose twice daily with 300 mg ATV plus 100 mg RTV.
Darunavir (DRV, ™C114, Prezista®)	No dosing guidelines for children. No dosing guidelines for adults.	Pediatric: Not approved for use in children <18 years. Currently under the study in PACTG/IMPAACT 1020 A. Adolescent ≥18 years/adults: 600 mg/dose DRV plus 100 mg RTV twice daily. DRV should not be used without RTV. Combination ART (adults): • Co-administration with MVC requires 150 mg MVC dose DRV 600 mg plus 100 mg RTV, all twice daily.
Fosamprenavir (f-AMP, Lexiva™)	No dosing guidelines for children. Adults—700 mg f-AMP plus 100 mg RTV twice daily.	Pediatric >6 and <18 years: in *treatment-naive* patients—30 mg/kg/dose (maximal dose, 1,400 mg, can be used in patients with body weight ≥47 kg) twice daily without RTV or 18 mg/kg/dose (maximal dose, 700 mg, can be used in patients with body weight ≥39 kg) plus RTV 3 mg/kg/dose (maximal dose, 100 mg) twice daily (can be used in patients with body weight ≥33 kg). In *treatment-experienced* patients—18 mg/kg/dose (maximal dose, 700 mg, can be used in patients with body weight ≥39 kg) plus RTV 3 mg/kg/dose (maximal dose, 100 mg, can be used in patients with body weight ≥33 kg) twice daily. Adults[d]: in *treatment-naive* patients—1,400 mg/dose twice daily without RTV or 700 mg plus 100 mg RTV both twice daily or 1,400 mg plus 200 mg RTV or 100 mg RTV both given once daily. In *treatment-experienced* patients—700 mg plus 100 mg RTV twice daily. Only boosted f-AMP with RTV should be used in treatment-experienced patients. Combination ART (adults):

Drug	WHO guidelines	US guidelines
		• Co-administration with EFV requires f-AMP dose of 700 mg plus 100 mg RTV twice daily or 1,400 mg f-AMP plus 300 mg RTV once daily. • Only boosted f-AMP should be used in combination with EFV. • Co-administration with MVC requires 150 mg MVC dose twice daily in combination with 700 mg f-AMP plus 100 mg RTV twice daily.
Indinavir (IDV, Crixivan®)	No dosing guidelines for children. Adults—800 mg IDV plus 100 mg RTV twice daily.	Pediatric: Not approved for use in children. Investigational dose of 500 mg/m^2 of body surface area every 8 hours (three times daily) in children 4–15 years of age resulted in adequate AUC and low plasma IDV trough. Adolescent >18 years/adults: 800 mg/dose every 8 hours. Adult dose in combination with RTV—800 mg IDV plus 100 mg RTV twice daily. Combination ART(adults): • Co-administration with EFV requires 800 mg IDV plus 100 or 200 mg RTV twice daily.
Lopinavir/ritonavir (LPV/RTV, Kaletra, ABT 378)	Body weight 14–39.9 kg—10 mg LPV/kg/dose twice daily (equivalent to 300 LPV mg/m^2). Body weight 15–40 kg—2.5 mg RTV/kg/dose twice daily (equivalent to 75 mg/m^2). Maximal dose—400 mg LPV plus 100 mf RTV twice daily. Adults/combination ART—capsules (133.3 mg LPV/33.3 mg RTV) 3 capsules twice daily or 4 capsules twice daily when co-administered with EFV (600 mg once daily) or NVP (150 mg twice daily); tablets (200 mg LPV/100 mg RTV) for *treatment-naive patients*—2 tablets twice daily, for *treatment-experienced patients*—3 tablets twice daily when co-administered with EFV (600 mg once daily) or NVP (150 mg twice daily).	Pediatric: body weight >15–<40 kg—10 mg/kg LPV/2.5 mg/kg RTV twice daily with food. Approximately equivalent to 230 mg/m^2 LPV/57.5 mg/m^2 RTV per dose. Body weight >40 kg—400 mg or 230 mg/m^2 LPV/57.5 mg/m^2 RTV per dose (maximal dose, 400 mg LPV/100 mg RTV). Use of 230 mg/m^2 LPV dose provides adequate AUC for LPV, but might produce lower trough, higher doses may be considered. Adolescent >12 years: 400 mg LPV/100 mg RTV per dose twice daily with food. Adolescent >18 years/adults: in antiretroviral naive patients—800 mg LPV/200 mg RTV per dose once daily. Combination ART (adolescents >12 years/adults): • Once daily dose should not be used in patients with concomitant therapy with EFV, NVP, f-AMP or NFV. • Co-administration with NVP, EFV or f-AMP requires increase in LPV/RTV dose to 300 mg/m^2 LPV/75 mg/m^2 RTV per dose in children <12 years of age and 600 mg LPV/150 mg RTV per dose twice daily with food. Combination ART (adults): • Co-administration with SQV requires 1,000 mg SQV dose without additional RTV twice daily with twice daily 400 mg LPV/100 mg RTV. • Co-administration with MVC requires 150 mg MVC dose with 400 mg LPV/100 mg RTV, all twice daily.
Nelfinavir (NFV, Viracept®)	Body weight ≥20 kg—maximum recommended dose of 1,250 mg/dose twice daily. Adults—1,250 mg/dose twice daily.	Pediatric <13 years: 45–55 mg/kg/dose twice daily or 25–35 mg/kg/dose three times daily. Adolescent/adults: 1,250 mg/dose twice daily or 750 mg/dose three times daily.
Ritonavir (RTV, Norvir®)	Children <16 years—400 mg/m^2/dose (maximal dose, 600 mg) twice daily. Scale up the dosing schedule at initiation starting at 250 mg/m^2/dose of body surface area twice daily with increments by 50 mg/m^2/dose at 2- to 3-day intervals to full dose as tolerated. As a booster for LPV for body weight	Pediatric: 350–450 mg/m^2/dose (maximal dose, 600 mg) twice daily. Scale up the dosing schedule at initiation starting at 250 mg/m^2/dose twice daily with increments by 50 mg/m^2 at 2- to 3-day intervals to full dose as tolerated. Adolescent/adults: 600 mg/dose twice daily. Scale up the dosing schedule at initiation starting at 300 mg/dose twice daily; and in stepwise increase until full dose is reached over 5 days as tolerated. Combination ART (adolescents/adults):

Drug	WHO guidelines	US guidelines
	15–40 kg—2.5 mg/kg/dose twice daily. No dosing guidelines for adults.	• RTV is used at lower doses as a pharmacokinetic enhancer to other PIs with doses ranging from 100 to 400 mg.
Saquinavir (SQV, Invirase®)	Not licensed for use in children <16 years of age or less than 25 kg. Never should be taken unboosted. Adults—1,000 mg SQV plus 100 mg RTV twice daily.	Pediatric: Not approved for use in children. Investigational dose of 50 mg/kg/dose every 8 hours (three times daily) provided inadequate AUC and plasma trough. Co-administration with RTV, LPV/RTV and NFV is being investigated. Adolescent >16 years/adults: 1,000 mg plus 100 mg RTV twice daily. Never should be used unboosted. Combination ART (adults): • Co-administration with LPV/RTV requires 1,000 mg SQV dose without additional RTV twice daily with twice daily 400 mg LPV/100 mg RTV. • Co-administration with MVC requires 150 mg MVC dose with 1,000 mg SQV plus 100 mg RTV, all twice daily.
Tipranavir (TPV, Aptivus®)	No dosing guidelines for children. No dosing guidelines for adults.	Pediatric: Not approved for use in children. Currently under study in PACTG1051/BI1182.14. Adult dose[d]: 500 mg plus 200 mg RTV twice daily. Combination ART (adults): • Co-administration with MVC requires 300 mg MVC dose with 500 mg TPV plus 200 mg RTV, all twice daily.
Maraviroc (MVC, Selzentry®)	No dosing guidelines for children. No dosing guidelines for adults.	Pediatric: Not approved for use in children <16 years. No data currently available on dosage below this age. Combination ART (adolescents/adults): When given with CYP3A4 inhibitors (with or without CYP3A4 inducers) including all PIs (except TPV/RTV)—150 mg/ dose twice daily. When given with other drugs that are not strong inhibitors or inducers of CYP3A4, such as NRTIs, T-20, TPV/RTV, and NVP—300 mg/dose twice daily. When given with CYP3A4 inducers including EFV—600 mg/dose twice daily.[e]
Enfuvirtide (Fuzeon™, T-20) Fusion Inhibitor	No dosing guidelines for children. No dosing guidelines for adults.	Pediatric: 2 mg/kg (maximal dose, 90 mg [1 ml]) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen. Adolescent >16 years/adults: 90 mg (1 ml) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.
Raltegravir (MK-0518, RGV, RAL, Insentress®)	No dosing guidelines for children. No dosing guidelines for adults.	Pediatric: Not approved for children <16 years. Currently in phase I/II study in IMPAACT P1066 for children aged 2–18 years. Adolescent >16 years/adults: 400 mg/dose twice daily.

The recommended doses are taken verbatim from the public-domain guidelines available at http://www.who.int/hiv/pub/guidelines/art/en/index.html and http://aidsinfo.nih.gov/Guidelines, respectively.

ART, antiretroviral therapy; AUC, area under the curve; CYP3A4, cytochrome P450 3A4; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials; PACTG, Pediatric AIDS Clinical Trials Group; PI, protease inhibitor; PK, pharmacokinetic; WHO, World Health Organization.

[a] Both weight and age are used to define “adolescent” patient. In certain references neither is used and “adolescent” is referred to as a category.

[b] The table does not provide food requirements or the dosing recommendations for patients with hepatic and renal insufficiency. Please refer to the actual guidelines available online at: http://www.who.int/hiv/pub/guidelines/art/en/index.html and http://aidsinfo.nih.gov/Guidelines.

[c] Pediatric doses for younger children and neonates and infants are not represented in the table.

[d] No adolescent dose is referenced in the guidelines.

[e]The list of other than ARV drugs considered for the Maraviroc (MVC) dose adjustment is available under Pediatric HIV Guidelines at http://aidsinfo.nih.gov/Guidelines.