Handbook of Pediatric HIV Care

This portable and practical handbook provides a concise guide to the essentials of pediatric HIV care. During the past few years, many agents for the treatment and prophylaxis of HIV infection and the opportunistic infections that accompany HIV infection have been developed, and many new ways of monitoring HIV infection in children have been produced. These new therapies and approaches to management are complicated, but the long-term health of HIV-infected children depends on their correct application. This handbook presents the core information and guidelines necessary for effective management of infected children.

Dr. Stephen L. Zeichner received his undergraduate and graduate degrees at the University of Chicago. He trained in pediatrics and infectious diseases at the Children’s Hospital of Philadelphia. An investigator in the HIV and AIDS Malignancy Branch, National Cancer Institute, NIH, and an adjunct family member of the George Washington University School of Medicine, Children’s National Medical Center, Washington, DC, and the Uniformed Services University of the Health Sciences, he studies the basic biology of HIV and Kaposi’s sarcoma-associated herpesvirus, and directs clinical trials of new therapies for HIV-infected children.

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For Rachel, Sarah, and Elizabeth

For Alex, Samantha, and Geoffrey
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Abbreviations

AAP  American Academy of Pediatrics
ABC  abacavir
ABCD  amphotericin B colloidal dispersion
ABLC  amphotericin B lipid complex
ACCAP  AIDS Community Care Alternatives Program
ACEI  angiotensin enzyme inhibitors
ACIP  Advisory Committee on Immunization Practices
ACOG  American College of Obstetricians and Gynecologists
ACTG  AIDS Clinical Trials Group
ACTH  adrenocorticotropin hormone
ACTIS  AIDS Clinical Trials Information Service
ADCC  antibody-dependent cell-mediated cytotoxicity
ADDP  AIDS Drug Distribution Program
ADEC  Association for Death Education and Counseling
ADHD  attention deficit/hyperactivity disorder
AEGIS  AIDS Education Global Information System
AFB  acid-fast bacilli
AFXB  Association François-Xavier Bagnoud
AGCUS  atypical glandular cells of undetermined significance
AIDS  acquired immune deficiency syndrome
ALRI  acute lower respiratory tract infection
AmFAR  American Foundation for AIDS Research
AMP  amprenavir
ANC  absolute neutrophil count
ANRS  Agence Nationale de Recherches sur le SIDA
AOM  acute otitis media
ACP  antigen-presenting cell
APV  amprenavir
ARB  angiotensin blockers
ARDS  acute respiratory distress syndrome
List of abbreviations

ARF acute renal failure
ARL AIDS-related lymphoma
ARN acute retinal necrosis
ART antiretroviral therapy
ASCUS atypical squamous cells of undetermined significance
AST aspartate aminotransferase
ATN adolescent medicine trials network
ATP adenosine triphosphate
ATZ atazanavir
AUC area under the curve
AZT zidovudine (also known as ZDV)
BAL bronchoalveolar lavage
BBB blood-brain barrier
BCG Bacille Calmette–Guerin
βHCG serum beta human chorionic gonadotropin
BIA bioelectrical impedance analysis
BMC bone mineral content
BMD bone mineral density
BMI body mass index
BUN blood urea nitrogen
BV bacterial vaginosis
CARE Ryan White (Comprehensive AIDS Resources Emergency) Act
CAT computerized axial tomography
CBC complete blood count
CD cluster of differentiation
CDC Centers for Disease Control and Prevention
CDC-GAP Centers for Disease Control and Prevention Global AIDS Program
CHF congestive heart failure
Cho choline
CHOP cyclophosphamide, doxorubicin, vincristine and prednisone
CIN cervical intraepithelial neoplasia
CIPRA Comprehensive International Program of Research on AIDS
Cmax maximum concentration/peak blood concentration
CMT cervical motion tenderness
CMV cytomegalovirus
CNS central nervous system
CPAP continuous positive airway pressure
CRF case report form
CRH corticotropin-releasing hormone
CRP C-reactive protein
List of abbreviations

CSF  cerebrospinal fluid
CSOM  chronic suppurative otitis media
CT  computed tomography
CTL  cytotoxic T-lymphocytes also cytotoxic memory T-cells
CVC  central venous catheter
CXR  chest X-ray
d4T  stavudine
DC  dendritic cells
DC-SIGN  dendritic cell–specific intercellular adhesion molecule–grabbing non-integrin
ddC  zalcitabine
dDI  didanosine
DEXA  dual energy X-ray absorptiometry
DFA  direct fluorescent antibodies also direct immunofluorescence assay
DHEAS  dihydroepiandrosterone sulfate
DHFR  dihydrofolate reductase
DHPS  dihydropteroate synthase
DHSS  Department of Health and Human Services
DIC  disseminated intravascular coagulation
DLBCL  diffuse large B-cell lymphoma
DLCO  diffusing capacity
dEL  delavirdine
DMAC  disseminated Mycobacterium avium complex
DMAPP  depot medroxyprogesterone acetate
DNA  deoxyribonucleic acid
dNTPs  triphosphorylated nucleosides
DOT  directly observed therapy
DOTS  directly observed therapy (short course)
DSMB  Data Safety Monitoring Board
DTH  delayed type hypersensitivity
DTP  diphtheria–tetanus–pertussis
DTaP  diphtheria–tetanus–acellular pertussis
DUB  dysfunctional uterine bleeding
EBCT  electron beam computed tomography
EBV  Epstein–Barr virus
EC  emergency contraception also enteric coated
ECG  electrocardiogram
ECHO  echocardiography
ED  Emergency Department also end diastolic
List of abbreviations

EEG electroencephalogram
EFV efavirenz
EGPAF Elisabeth Glaser Pediatric AIDS Foundation
EGW external genital warts
EIA enzyme immunoassay
ELISA enzyme-linked immunosorbent assays
EMEA European Agency for the Evaluation of Medicinal Products
ENF enfuvirtide
Env viral envelope
EP extrapulmonary pneumocytosis
ERCP endoscopic retrograde cholangiopancreatography
ES end systolic
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
5-FU 5-fluorouracil
FACS fluorescent antibody cell sorting
FAMA fluorescent antibody membrane antigen
FDA Food and Drug Administration
FEV₁ forced expiratory volume in 1 second
FFA free-fatty acids
FFM fat free mass
FRS fat redistribution syndrome
FSGS focal segmental glomerulosclerosis
FSH follicle stimulating hormone
FTC emtricitabine
FTT failure to thrive
FVC forced vital capacity
G-6-PD glucose-6-phosphate dehydrogenase
GCP good clinical practices
g-CSF filgrastim
G-CSF granulocyte-colony stimulating factor
GER gastroesophageal reflux
GH growth hormone
GI gastrointestinal
GM-CSF granulocyte-macrophage colony-stimulating factor
GnRH gonadotropin releasing hormone
HAART highly active antiretroviral therapy
HABAN hyperandrogenic-insulin resistant acanthosis nigricans
HAMB HIV and AIDS Malignancy Branch
List of abbreviations

HAM/TSP  HLTV-1-associated myelopathy/tropical spastic paraparesis
HAV  hepatitis A virus
HAZ  height-for-age Z-scores
hbhA  heparin-binding hemagglutinin adhesin
HBIG  hepatitis B immunoglobulin
HBV  hepatitis virus B
HCP  healthcare personnel
HDL  high-density lipoprotein
HDL-C  high-density lipoprotein cholesterol
HHV-6  human herpesvirus-6
HHV-8  human herpesvirus-8
HIB  Hemophilus influenzae type B
HIV  human immunodeficiency virus
HLA  human leukocyte antigen
HMOs  health maintenance organizations
1HMRS  proton magnetic resonance spectroscopy
HBA  hypothalamic-pituitary-adrenal
HPTN  HIV Prevention Trials Network
HPV  human papillomavirus
HRCT  high-resolution computerized tomography
HRIG  human rabies immunoglobulin
HSI  HIV/AIDS and sexually transmitted infections
HSV  herpes simplex virus
HTLV-1  human T-cell leukemia virus 1
HUS  hemolytic-uremic syndrome
ICASO  International Council of AIDS Services Organizations
ICD  immune complex dissociated
ICMA  immunochemiluminescent assay
IDU  injection drug use
IDV  indinavir
IFA  immunofluorescence assay
IFN  interferon
Ig  immunoglobulin
IGFBP-3  insulin-like growth factor binding protein-3
IGFBPs  IGF binding proteins
Igf-1  insulin-like growth factor 1
IL  interleukin
ILD  interstitial lung disease
IMCI  integrated management of childhood illness
INH  isoniazid
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>ln V</td>
<td>intravaginal</td>
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<td>IP</td>
<td>interferon inducible protein</td>
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<td>IPAA</td>
<td>International Partnership Against AIDS</td>
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<td>IPI</td>
<td>invasive pneumococcal infections</td>
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<td>IPV</td>
<td>inactivated polio vaccine</td>
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<td>IQ</td>
<td>inhibitory quotient</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<td>IRU</td>
<td>immune recovery uveitis</td>
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<td>ISA</td>
<td>induced sputum analysis</td>
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<tr>
<td>ITP</td>
<td>immune thrombocytopenia purpura</td>
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<td>IUDs</td>
<td>intrauterine devices</td>
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<td>IUS</td>
<td>intrauterine system</td>
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<tr>
<td>IVIG</td>
<td>intravenous immunoglobulin</td>
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<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
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<tr>
<td>KS</td>
<td>Kaposi's sarcoma</td>
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<td>KSHV</td>
<td>Kaposi's sarcoma-associated herpesvirus</td>
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<tr>
<td>LBM</td>
<td>lean body mass</td>
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<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
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<td>LDL</td>
<td>low-density lipoproteins</td>
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<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
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<td>LFT</td>
<td>liver function test</td>
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<tr>
<td>LGE</td>
<td>linear gingival erythema</td>
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<td>LH</td>
<td>luteinizing hormone</td>
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<tr>
<td>LIFE</td>
<td>leadership and investment in fighting an epidemic</td>
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<tr>
<td>LP</td>
<td>lymphoid interstitial pneumonitis</td>
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<td>LIPA</td>
<td>line probe assays</td>
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<tr>
<td>LP</td>
<td>lumbar puncture</td>
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<td>LPN</td>
<td>licensed practical nurse</td>
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<tr>
<td>LPV</td>
<td>lopinavir</td>
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<td>LPV/r</td>
<td>lopinavir plus ritonavir</td>
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<tr>
<td>LTNP</td>
<td>long-term non-progression</td>
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<tr>
<td>ITR</td>
<td>long terminal repeat (HIV promotor)</td>
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<tr>
<td>IV</td>
<td>left ventricular</td>
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<tr>
<td>MAC</td>
<td>Mycobacterium avium complex also mid-arm circumference</td>
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<tr>
<td>MACS</td>
<td>Multicenter AIDS Cohort Study</td>
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<tr>
<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
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<td>MAMC</td>
<td>mid-arm muscle circumference</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NUG</td>
<td>necrotizing ulcerative gingivitis</td>
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<td>NUP</td>
<td>necrotizing ulcerative periodontitis</td>
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<tr>
<td>N/V</td>
<td>nausea/vomiting</td>
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<tr>
<td>17-OHP</td>
<td>17-hydroxyprogesterone</td>
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<tr>
<td>OCs</td>
<td>oral contraceptives</td>
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<td>OD</td>
<td>optical density</td>
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<td>OGTT</td>
<td>oral glucose tolerance test</td>
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<td>OHL</td>
<td>oral hairy leukoplakia</td>
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<td>OHRP</td>
<td>Office of Human Research Protections</td>
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<tr>
<td>OIs</td>
<td>opportunistic infections</td>
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<tr>
<td>OLA</td>
<td>oligonucleotide ligation assays</td>
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<tr>
<td>oPEP</td>
<td>occupational postexposure prophylaxis</td>
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<td>OPV</td>
<td>oral polio vaccine</td>
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<td>OSHA</td>
<td>Occupational Safety and Health Administration</td>
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<td>PACTG</td>
<td>Pediatric AIDS Clinical Trials Group</td>
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<td>PACTS</td>
<td>Perinatal AIDS Collaborative Transmission Study</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PAP</td>
<td>Papanicolaou (Smear)</td>
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<tr>
<td>PBDL</td>
<td>polymorphic B-cell lymphoproliferative disorder</td>
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<td>PBMC</td>
<td>peripheral blood mononuclear cells</td>
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<td>PCM</td>
<td>protein–calorie malnutrition</td>
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<tr>
<td>FNS</td>
<td>primary central nervous system</td>
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<tr>
<td>PCLS</td>
<td>polycystic ovary syndrome</td>
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<tr>
<td>PCL</td>
<td>Pneumocystis jiroveci pneumonia also primary healthcare provider</td>
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<tr>
<td>P Cr</td>
<td>plasma creatinine</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>PCV</td>
<td>pneumococcal conjugate vaccine</td>
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<tr>
<td>PCV7</td>
<td>heptavalent pneumococcal conjugate vaccine</td>
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<tr>
<td>PEL</td>
<td>primary effusion lymphoma</td>
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<tr>
<td>PENTA</td>
<td>The Pediatric European Network for the Treatment of AIDS</td>
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<tr>
<td>PEP</td>
<td>postexposure prophylaxis</td>
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<tr>
<td>PFC</td>
<td>persistent fetal circulation</td>
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<tr>
<td>PFTs</td>
<td>pulmonary function tests</td>
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<tr>
<td>PGE2</td>
<td>prostaglandin E2</td>
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<tr>
<td>PGP</td>
<td>p-glycoprotein</td>
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<tr>
<td>PHA</td>
<td>phytohemagglutinin</td>
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<tr>
<td>PHC</td>
<td>preventive health care</td>
</tr>
<tr>
<td>PHS</td>
<td>public health service</td>
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<tr>
<td>Pi</td>
<td>pentamidine isothionate</td>
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<tr>
<td>Ps</td>
<td>protease inhibitors</td>
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List of abbreviations

PIC  pre-integration complex
PID  pelvic inflammatory disease
PIT  pills identification test
PJ  P. jiroveci
PLH  pulmonary lymphoid hyperplasia
PMDD  premenstrual dysphoric disorder
PML  progressive multifocal leukoencephalopathy
PMPA  9-[(2-[(R)-(phosphonylmethoxy)propyl] adenine
PMDD  premenstrual dysphoric disorder
PMTCT  prevention of mother-to-child transmission
PNa  plasma sodium
PNS  peripheral nervous system
PORN  progressive outer retinal necrosis
POS  point of service
PPD  purified protein derivative
PPD  preferred providers organizations
PPV  pneumococcal polysaccharide vaccine
PMN  polymorphonuclear leukocyte
PRA  peripheral renin activity
PRAMS  pregnancy risk assessment monitoring system
PSD  Pediatric Spectrum of Disease
PT  prothrombin time
PTh  parathyroid hormone
PTT  partial thromboplastin time
PTX  spontaneous pneumothorax
PWAs  persons with AIDS
PZA  pyrazinamide
RAD  reactive airway disease
RBC  red blood cells
RDA  recommended dietary allowance
REACH  reaching for excellence in adolescent care and health
REM  rough endoplasmic reticulum
RN  registered nurse
RNA  ribonucleic acid
ROsPA  recombinant outer surface protein
RPE  retinal pigment epithelium
RR  relative risk
REE  rev responsive element
RSP  respiratory syncytial virus
RTI  reverse transcriptase inhibitor
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>RT-PCR</td>
<td>reverse transcription-polymerase chain reaction</td>
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<tr>
<td>RTV</td>
<td>ritonavir</td>
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<tr>
<td>SBIs</td>
<td>serious bacterial infections</td>
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<tr>
<td>Sc</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SDF</td>
<td>stromal-cell derived factor</td>
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<tr>
<td>SHBG</td>
<td>sex hormone-binding globulin</td>
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<tr>
<td>SADH</td>
<td>syndrome of inappropriate secretion of antidiuretic hormone</td>
</tr>
<tr>
<td>SILs</td>
<td>squamous intraepithelial lesions</td>
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<tr>
<td>siRNA</td>
<td>small interfering ribonucleic acids</td>
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<tr>
<td>SIV</td>
<td>simian immunodeficiency virus</td>
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<tr>
<td>SMM</td>
<td>Sooty Mangabey monkey</td>
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<tr>
<td>SOIs</td>
<td>sharp object injuries</td>
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<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
</tr>
<tr>
<td>SPNS</td>
<td>special projects of national significance</td>
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<tr>
<td>SQV</td>
<td>saquinavir</td>
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<tr>
<td>SSI</td>
<td>Social Security Disability Income</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>STIs</td>
<td>sexually transmitted infections</td>
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<tr>
<td>SUIDS</td>
<td>single use diagnostic system</td>
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<tr>
<td>3TC</td>
<td>lamivudine</td>
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<tr>
<td>T4</td>
<td>free levothyroxine</td>
</tr>
<tr>
<td>TAMs</td>
<td>thymidine analogue mutations</td>
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<tr>
<td>TANF</td>
<td>temporary assistance for needy families</td>
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<tr>
<td>TAR</td>
<td>transactivation responsive</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>TCA</td>
<td>trichloroacetic acid</td>
</tr>
<tr>
<td>TCR</td>
<td>t-cell receptors</td>
</tr>
<tr>
<td>Td</td>
<td>tetanus and diphtheria toxoids</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>TDM</td>
<td>therapeutic drug monitoring</td>
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<tr>
<td>Th</td>
<td>T-helper</td>
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<tr>
<td>TIG</td>
<td>tetanus immunoglobulin</td>
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<tr>
<td>TMP/SMX</td>
<td>trimethoprim-sulfamethoxazole</td>
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<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
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<tr>
<td>TOA</td>
<td>tubo-ovarian abscess</td>
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<tr>
<td>TPN</td>
<td>total parenteral nutrition</td>
</tr>
<tr>
<td>TREAT</td>
<td>treatment regimens enhancing adherence in teens</td>
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<tr>
<td>TRH</td>
<td>thyrotropin-releasing hormone</td>
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</tbody>
</table>
List of abbreviations

TSF triceps skinfold thickness
TSH thyroid stimulating hormone
TST tuberculin skin test
TTP thrombotic thrombocytopenia purpura
U Cr urine creatinine
UDPGT uridine diphosphoglycronyltransferase
U Na urine sodium
URIs upper respiratory infections
USAD United States Agency for International Development
USPHS United States Public Health Service
UTI urinary tract infection
VCAM-1 vascular cell adhesion molecule-1
VGC valganciclovir
VLA-4 very late activation antigen-4
Vif virion infectivity factor
VLDL very low density lipoprotein
VZIG varicella-zoster immunoglobulin
VZV varicella-zoster virus
WAZ weight-for-age Z-scores
WBCs white blood cells
VVC vulvovaginal candidiasis
WHO World Health Organization
WITS Women and Infants Transmission Study
XR extended release
ZDV zidovudine (also known as AZT)
More than two decades have passed since this devastating infection was first identified. We have come from a time when no diagnosis could be made and there was no treatment, to an era when the development of multiple therapeutic agents and advances in the prevention of HIV infection is commonplace in the developed world. Foremost amongst these accomplishments is our ability to prevent mother-to-child transmission of HIV infection. Seldom is it possible to chronicle such advances in knowledge, which materially affect the lives of thousands of people on a daily basis. All of this speaks to the commitment of scientists and care providers and the rapid evolution of information and technology. There is, however, a pervasive recurrent theme of needing to advocate for the health of children infected and affected by HIV infection.

This handbook provides accessible information at a time when the developed world has succeeded in dramatically decreasing the number of children who acquire infection from their mothers. The need for this information is greater now than ever before. First, because the evolution of information continues at a rapid rate. Second, because the complexity of treatment requires expertise and access to the most current information. Third, because the numbers of HIV-infected children have decreased in the USA and the probability that a physician will have cumulative experience with substantive numbers of these children has diminished. It is important that pediatricians continue to be sensitive to the possibility that a child is HIV-infected and be attuned the specific medical needs and support systems required.

There is an index to Web sources of information, convenient summary tables, and eloquent discussions of antiretroviral drugs conveniently separated from therapeutic decision making. The material is readable, concise, and thorough.

I would wish that this information was accessible, in demand, and essential in the parts of the world where there is so much HIV infection of adults and children. One must reflect on the fact that as many infants are born with HIV infection in sub-Saharan Africa every day as were born in the USA in an entire year prior to the availability of interventions to prevent mother-to-child transmission. Progress is being made to bring...
these effective interventions to the developing world. We would hope we can entice a new generation of pediatricians, public health authorities, and other providers to devote their lives to addressing the problem as effectively in the developing world as has been done in the developed world. This handbook contributes to the knowledge, and hopefully will provide additional incentive to take these advances to the entire world of children.
Preface

When Cambridge University Press decided to undertake the publication of the second edition of the *Handbook of Pediatric Care*, they told us that they were very enthusiastic about the book, but that they thought that, while the handbook was too large to be a true “handbook,” they still valued and appreciated the more comprehensive content of the book. The Press therefore asked us, for the second edition, to both shorten the material to a more manageable size to make a new handbook and to augment the material in the handbook to make an even more comprehensive *Textbook of Pediatric HIV Care*. We hope that we have achieved these goals in these two books, a second edition of the *Handbook of Pediatric HIV Care* and the first edition of the *Textbook of Pediatric HIV Care*.

Our goals for both books are to provide the clinician with the information needed to provide excellent care to children infected with HIV. Neither book is meant to be an exhaustive treatise on the subject of pediatric HIV disease, covering all the many societal and policy issues that are involved necessarily in a complete discussion of HIV and children. Rather, we aim to provide helpful management information for the frontline clinician. While we have focused on the management of pediatric HIV disease, we believe that effective management requires a solid understanding of the basic and applied virology, immunology, and pathophysiology of the disease, so that the practitioner can thoughtfully and rationally apply the management information supplied in the other chapters. Our authors have included more detailed discussions in their *Textbook* chapters, and have tried to condense their presentations in their *Handbook* chapters to include the most clinically pertinent details. Some of the information presented in more than one *Textbook* chapters has been condensed into a single chapter for the handbook, but we hope that we have been able to include the information in the handbook that will enable clinicians to provide optimum care for their HIV-infected patients.

The HIV epidemic changes quickly. The authors of the individual chapters have attempted to include a significant amount of new information, including new basic science findings, new information concerning the pathogenesis of the disease and the opportunistic infections that affect children with HIV, descriptions of recently
approved drugs and recently developed drugs that may be close to approval, both for HIV and for HIV-related opportunistic infections, new information concerning the management of children infected with HIV, and information concerning the social welfare of children infected with HIV. In some fields, so much new information has become available that we included entirely new chapters in the book. There are new chapters about the evolutionary biology of antiretroviral drug resistance and the assessment and management of antiretroviral drug resistance, the interruption of mother-to-infant HIV transmission, metabolic complications of HIV infection and antiretroviral therapy, therapeutic drug monitoring for HIV infection, and the gynecology of the HIV-infected adolescent. Neither book has chapters discussing, in detail, HIV vaccines because both prophylactic and therapeutic vaccines are only in the earliest stages of clinical development, but the basic science chapters about virology, immunology, pathogenesis, and natural history describe some of the fundamental information that vaccine developers are using in their efforts. We hope that we will be able to include in a future edition chapters that outline the use of prophylactic and therapeutic vaccines for HIV infection.

The book does not include a specific chapter on the management of pediatric HIV disease in resource-poor countries. We initially contemplated including such a chapter in the book, but soon came to realize that the spectrum of resources available in ‘resource-poor’ countries varied tremendously from one country to another. For example, in some countries there are government-mandated commitments to essentially universal access to antiretrovirals, while in others only a tiny fraction of the population has access to the drugs, and these circumstances are changing month by month. We look forward to the day when everyone will receive the best care possible, but until then we thought it wisest to describe state-of-the-art care as practiced in the world’s richer countries, and acknowledge that providers elsewhere will know best how to adapt these principles to their own local circumstances.