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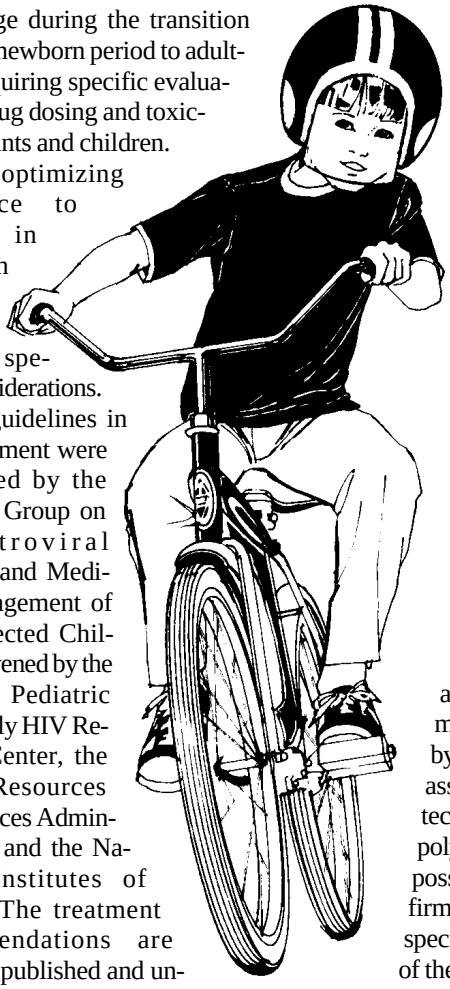
Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

The following article is adapted from the MMWR article with the above title (1998;47[No. RR-4]:1-43). If you would like to receive a copy of the entire MMWR article, you may call the Office of Epidemiology at 804/786-6261 or visit the Centers for Disease Control and Prevention web site at http://www.cdc.gov.

Background

Therapeutic strategies now focus on early institution of antiretroviral regimens capable of maximally suppressing viral replication to reduce the development of resistance and to preserve immunologic function. Although the pathogenesis of human immunodeficiency virus (HIV) infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected individuals, there are unique considerations in HIV-infected infants, children, and adolescents. Most HIV infections in children are acquired perinatally, and the majority of perinatal transmission occurs during or near the time of birth. This raises the possibility of initiating treatment in an infected infant during the period of initial (primary) HIV infection if sensitive diagnostic tests are used to define the infant's infection status early in life. Perinatal HIV infection occurs during the development of the infant's immune system; thus, both the clinical manifestations of HIV infection and the course of immunologic and virologic markers of infection differ from those for adults. Treatment of perinatally-infected children will occur in the context of prior exposure to zidovudine (ZDV) and other antiretroviral drugs used during pregnancy and the neonatal period for treating maternal infection and/or for preventing perinatal transmission. Additionally, drug pharmacokinetics change during the transition from the newborn period to adulthood, requiring specific evaluation of drug dosing and toxicity in infants and children. Finally, optimizing adherence to therapy in children and adolescents requires specific considerations.



The guidelines in this document were developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children convened by the National Pediatric and Family HIV Resource Center, the Health Resources and Services Administration, and the National Institutes of Health. The treatment recommendations are based on published and unpublished data on HIV infection and treatment in adults and children and, when no definitive data were available, the clinical experience of the Working Group members. The Working Group intended the guidelines to be flexible and not to supplant the clinical judgment of experienced health-care providers. These guidelines will need to be modified as new information and clinical experience become available.

Identification of Perinatal HIV Exposure

Appropriate treatment of HIV-infected infants requires the identification of HIV-exposed infants as soon as possible. This can be best accomplished through the identification of HIV-infected women before or during pregnancy. Universal HIV counseling and voluntary HIV testing with consent are recommended as the standard of care for all pregnant women in the United States by the U.S. Public Health Service, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists, and are endorsed by the Working Group.

Diagnosis of HIV Infection in Infants

HIV infection can be definitively diagnosed in most infected infants by age 1 month and in virtually all infected infants by age 6 months by using viral diagnostic assays. A positive virologic test (i.e., detection of HIV by culture or DNA or RNA polymerase chain reaction [PCR]) indicates possible HIV infection and should be confirmed by a repeat virologic test on a second specimen as soon as possible after the results of the first test are known. HIV DNA PCR is the preferred virologic method for diagnosing HIV infection in infancy. Diagnostic testing should be performed before the infant is aged 48 hours, at age 1-2 months, and at age 3-6 months. Testing at age 14 days also may be advantageous for early detection of infection. HIV-exposed infants should be evaluated by or in consultation with a pediatric HIV specialist.

HIV-exposed children who have had repeatedly negative virologic assays at birth and at age 1-2 months should be retested again at age 3-6 months. HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples. HIV infection can be reasonably excluded among children with two or more negative virologic tests, one performed at age ≥1 month and the other at age ≥4 months. Two or more negative HIV immunoglobulin G (IgG) antibody tests performed at age >6 months with an interval of at least 1 month between the tests can be used to reasonably exclude HIV infection. HIV infection can be definitively excluded if HIV IgG antibody is negative in the absence of hypogammaglobulinemia at age 18 months and if the child has no clinical symptoms of HIV infection and has negative HIV virologic assays.

Monitoring Pediatric HIV Infection

A pediatric clinical and immunologic staging system for HIV infection has been developed that includes age-related definitions of immune suppression (Tables 1 and 2). While the CD4+ absolute number that identifies a specific level of immune suppression changes with age, the CD4+ percentage that defines each immunologic category does not. Thus, a change in CD4+ percentage, not number, may be a better marker to identify disease progression in children. In infected children and adults, CD4+ cell count declines as HIV infection progresses, and patients with lower CD4+ cell counts have a poorer prognosis than patients with higher counts.

Treatment Recommendations

Initiation of Antiretroviral Therapy

When to Initiate Therapy

Antiretroviral therapy is recommended for HIV-infected children with clinical symptoms of HIV infection or evidence of immune suppression, regardless of age or viral load (Table 3). Pediatric and adult clinical trial data have demonstrated that antiretroviral therapy in symptomatic patients slows clinical and immunologic disease progression and reduces mortality.

Ideally, antiretroviral therapy should be initiated in all HIV-infected infants aged <12 months as soon as a confirmed diagnosis is established, regardless of clinical or immunologic status or viral load. HIV-infected infants aged <12 months are considered at high risk for disease progression and the predictive value of immunologic and virologic parameters to identify those who will have rapid progression is less than that for older children. Identification of infection during the first few weeks of life permits clinicians to initiate antiretroviral therapy or intensify ongoing antiretroviral therapy used for chemoprophylaxis of perinatal transmission during the initial phases of primary infection.

Two general approaches for initiating therapy in asymptomatic children aged ≥1 year were outlined by the Working Group. The first approach would be to initiate therapy in all HIV-infected children regardless of age or symptom status in order to treat infected children as early as possible in the course of disease and to intervene prior to immunologic deterioration.

An alternative approach would be to defer treatment in asymptomatic children aged ≥1 year with normal immune status in situations in which the risk for clinical disease progression is low (e.g., low viral load) and when other factors (e.g., concern for adherence, safety, and persistence of antiretroviral response) favor postponing treatment. In such cases, the health-care provider should regularly monitor virologic, immunologic, and clinical status. Factors to be considered in deciding when to initiate therapy include a) high or increasing HIV RNA levels, b) rapidly declining CD4+ T-lymphocyte number or percentage to values approaching those indicative of moderate immune suppression (i.e., immune category 2 [Table 1]), or c) development of clinical symptoms.

The level of HIV RNA considered indicative of increased risk for disease progression is not well defined in young children. Regardless of age, any child with HIV RNA levels >100,000 copies/mL is at high risk for mortality, and antiretroviral therapy should be initiated, regardless of clinical or immune status. HIV RNA levels in asymptomatic children aged ≥30 months that are the same as levels for which there are treatment recommendations for HIV-infected adults (e.g., >10,000-20,000 copies/mL) also may indicate the need to initiate treatment.

It is important that intensive education of the caregivers and patients about the importance of adherence to the prescribed treatment regimen be provided before therapy is initiated so that potential problems and solutions can be identified. Frequent follow-up should be provided to assess virologic response to therapy as well as drug tolerance and adherence.

Choice of Initial Antiretroviral Therapy

Combination therapy is recommended for all infants, children, and adolescents who are treated with antiretroviral agents (Table 4). Monotherapy with the currently available antiretroviral drugs is no longer recommended to treat HIV infection. ZDV monotherapy is appropriate, however, when used in infants of indeterminate HIV status during the first 6 weeks of life to prevent perinatal HIV transmission. Infants who are identified as being HIV-infected while receiving ZDV chemoprophylaxis should be changed to a combination antiretroviral drug regimen. Aggressive antiretroviral therapy for primary perinatal infection with three drugs is recommended because it provides the best opportunity to pre-

Table 1. 1994 Revised Pediatric HIV Classification System: Immunologic Categories Based on Age-Specific CD4+T-Lymphocyte Count and Percentage

	Age of Child					
Immune Category	<12 mos number/μL	(%)	1-5 yrs number/μL	(%)	6-12 yrs number/μL	(%)
Category 1: No suppression	≥1,500	(≥25%)	≥1,000	(≥25%)	≥500	(≥25%)
Category 2: Moderate suppression	750-1,499	(15-24%)	500-999	(15-24%)	200-499	(15-24%)
Category 3: Severe suppression	<750	(<15%)	<500	(<15%)	<200	(<15%)

serve immune function and delay disease progression.

Changing Antiretroviral Therapy

The following three reasons warrant a change in antiretroviral therapy: 1) failure of the current regimen with evidence of disease progression based on virologic, immunologic, or clinical parameters; 2) toxicity or intolerance to the current regimen; and 3) new data demonstrating that a drug or regimen is superior to the current regimen. Prior to initiation of new treatment, intensive family education and medication training should be completed.

Virologic Considerations for Changing Therapy

Ideally, antiretroviral therapy should maximally suppress viral replication to below levels capable of being detected with HIV RNA assays. This may not always be achievable. Perinatally infected children generally have high HIV RNA levels, and clinical benefit may be observed with decrements in HIV RNA levels that do not result in undetectable levels. However, failure to maximally suppress replication may be associated with increased probability of viral mutations and the emergence of drug resistance. Consideration of the implications of changing regimens and the choice of new drugs should include an acknowledgment of the potential for limiting the patient's future options for potent therapy.

Following achievement of a maximal virologic response, HIV RNA levels should be measured at least every 3 months to monitor continued response to therapy. At least two measurements taken 1 week apart should be performed before considering a change in therapy. The following situations may indicate a need for change in therapy in infected children:

1. Less than a minimally acceptable virologic response after 8-12 weeks of therapy. For children receiving antiretroviral therapy with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a protease inhibitor, such a response is defined as a <10-fold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels. For children who are receiving less potent antiretroviral therapy (i.e., dual NRTI combinations), an insufficient response is defined as a less than fivefold (0.7 $\log_{10}$) decrease in HIV RNA levels from baseline.
2. HIV RNA levels not suppressed to undetectable after 4-6 months of antiretroviral therapy.
3. Repeated detection of HIV RNA in children who had initially responded to antiretroviral therapy with undetectable levels. This suggests the development of resistance or problems with adherence or drug bioavailability.
4. A reproducible increase in HIV RNA copy number among children who have had a substantial HIV RNA response but still have low levels of detectable HIV RNA. Such an increase would warrant a change in therapy if, after initiation of the therapeutic regimen, a greater than threefold (>0.5 $\log_{10}$) increase in copy number is observed in children aged ≥2 years. Because of the greater biologic variability in RNA in young children, a change in therapy is warranted when a greater than fivefold (>0.7 $\log_{10}$) increase is observed in children aged <2 years.

Table 2. 1994 Revised Pediatric HIV Classification System: Clinical Categories

Category N: Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only **ONE** of the conditions listed in Category A.

Category A: Mildly Symptomatic

Children with **TWO** or more of the conditions listed below but none of those listed in Categories B and C.

- Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis or otitis media

Category B: Moderately Symptomatic

Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include, but are not limited to:

- Anemia (<8 gm/dL), neutropenia (<1,000/mm^3), or thrombocytopenia (<100,000/mm^3) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children aged >6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before age 1 month
- Diarrhea, recurrent or chronic
- Fever lasting >1 month
- Hepatitis
- Herpes simplex virus stomatitis, recurrent (i.e., more than 2 episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
- Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Toxoplasmosis with onset before age 1 month
- Varicella, disseminated (i.e., complicated chickenpox)

Category C: Severely Symptomatic

Children who have any condition listed in the 1987 surevillance case definition for acquired immunodeficiency syndrome, with the exception of LIP (which is a Category B condition).

Immunologic Considerations for Changing Therapy

CD4+ T-lymphocyte count and percentage are independent predictors of disease progression and mortality in HIV-infected children. Before considering changing antiretroviral therapy due to an apparent decline in CD4+ T-lymphocyte values, the change should be validated by at least one repeated measurement obtained at least one week after the initial test. The following are immunologic indications that may warrant a change in antiretroviral therapy for HIV-infected children:

1. Change in immune classification (Table 1). However, minimal changes in CD4+ percentile that may result in a change in immune category (e.g., from 26% to 24% or from 16% to 14%) may not be as concerning as a rapid substantial change in CD4+ percentile within the same immune category (e.g., a decrease from 35% to 25%).
2. For children with CD4+ percentages of <15%, a persistent decline of five percentiles or more in CD4+ cell percentage (e.g., from 15% to 10% or from 10% to 5%).
3. A rapid and substantial decrease in absolute CD4+ T-lymphocyte count (e.g., a >30% decline in <6 months).

Clinical Considerations for Changing Therapy

The occurrence of certain clinical events while receiving antiretroviral therapy is evidence of HIV disease progression and/or a poorer prognosis for infants and children. The following clinical criteria warrant consideration of a change in antiretroviral therapy:

1. Progressive neurodevelopmental deterioration (i.e., persistence or progression of deterioration documented on repeated testing as demonstrated by the presence of two or more of the following findings: brain growth impairment, cognitive function decline as documented by psychometric testing, or clinical motor dysfunction).
2. Growth failure (i.e., persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation).
3. Disease progression (i.e., advancement from one pediatric clinical category to another [Table 2]). Prognosis is poorer as patients progress to more advanced clinical categories.

Choosing a New Antiretroviral Regimen

The choice of a new antiretroviral regimen is dictated by the indications that warranted the change in therapy and the limited number of available alternative antiretroviral agents. New regimens should be chosen partly on the basis of the impact of the changes on future treatment options.

The following principles should be followed when choosing a new antiretroviral regimen in children who have received prior treatment:

1. When changing therapy because of toxicity or intolerance, agents with different toxicity and side-effect profiles should be chosen, when possible.
2. When changing therapy because of treatment failure, adherence to therapy should be assessed as a potential cause of failure.
3. If the patient is adherent to the prescribed drug regimen, assume the development of drug resistance and, if possible, change at least two drugs to new antiretroviral agents. Change in a single drug or addition of a single drug to a failing regimen is suboptimal. The new regimen should include at least three drugs, if possible. Potential cross-resistance between antiretroviral drugs should be considered in choosing new drugs.
4. When considering changing to a new regimen, all other medications taken by the patient should be reviewed for possible drug interactions.
5. A change to a new regimen, especially one containing protease inhibitors, must include a discussion of treatment adherence issues between the caregivers of the infected child and the health-care provider. The health-care provider must recognize that certain medications are difficult to take in combination because of exacting and often conflicting requirements with respect to whether or not they can be taken with food and other antiretrovirals.
6. When changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life must be considered.

Table 3. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children*

1. Clinical symptoms related to HIV infection (i.e., Clinical Category A, B, or C [Table 2].)
2. Evidence of immune suppression, as indicated by CD4+ T-lymphocyte absolute number or percentage (i.e., Immune Category 2 or 3 [Table 1].)
3. All HIV-infected infants aged <12 months regardless of clinical, immunologic or virologic status.
4. For asymptomatic children aged ≥1 year with normal immune status, two options can be considered:
   - Preferred Approach - Initiate therapy in all HIV-infected children regardless of age or symptom status.
   - Alternate Approach - Defer treatment in situations in which the risk of clinically significant disease progression is low and other factors (e.g., concern for the durability of response, safety, and adherence) favor deferring treatment. In such cases, clinical, immunologic and virologic status should be closely monitored. Factors that should be considered in deciding to initiate therapy include:
     - → High or increasing HIV RNA copy number
     - → Rapidly declining CD4+ lymphocyte number or percentage to values approaching those indicative of moderate immune suppression (i.e., Immune Category 2 [Table 1])
     - → Development of clinical symptoms

**Indications for initiation of antiretroviral therapy in post-pubertal HIV-infected adolescents should follow the adult guidelines. (See Virginia Epidemiology Bulletin, June 1998.)*

Special Issues in Treatment of HIV-Infected Children

1. Adherence to drugs is especially problematic for children. Infants and young children are dependent upon others for administration of medication; thus, assessment of the capacity for adherence to a complex multidrug regimen requires evaluation of the caregivers and their environments and the ability and willingness of the child

Table 4. Recommended Antiretroviral Options for Initial Therapy of Pediatric HIV Infection

Preferred Regimen (Evidence of clinical benefit and sustained suppression of HIV RNA in clinical trials in infected adults; studies in pediatric patients are ongoing):

One highly active protease inhibitor plus two nucleoside analogue reverse transcriptase inhibitors (NRTIs)

⇒ Protease inhibitor:

Preferred protease inhibitor for infants and children who cannot swallow pills or capsules: Nelfinavir or Ritonavir

Alternative for children who can swallow pills: Indinavir

⇒ Recommended dual NRTI combinations:*

Most data on use in children:	ZDV + dideoxyinosine (ddI)
	ZDV + lamivudine (3TC)
More limited data on use in children:	stavudine (d4T) + ddI
	d4T + 3TC
	ZDV + zalcitabine (ddC)

Alternative Regimens (Less likely to produce sustained HIV RNA suppression in infected adults; in a small preliminary study, the combination of nevirapine, ZDV and ddI produced substantial and sustained suppression of viral replication in two of six infants first treated at age <4 months):

Nevirapine§ + 2 NRTIs (as above)

Secondary Alternative Regimen (Clinical benefit demonstrated in clinical trials involving infected adults and/or children, but initial viral suppression may not be sustained):

2 NRTIs (one of the recommended dual NRTI combinations listed above)

Not Recommended (Evidence against use due to overlapping toxicity and/or because use may be virologically undesirable):

Any monotherapy¶	d4T + ZDV
ddC + ddI	ddC + d4T
ddC + 3TC	

**ddC is not available in a liquid preparation commercially, although a liquid formulation is available through a compassionate use program of the manufacturer (Hoffman-LaRoche Inc., Nutley, New Jersey). ZDV and ddC is a less preferred choice for use in combination with a protease inhibitor.*
§A liquid preparation of nevirapine is not available commercially, but is available through a compassionate use program of the manufacturer (Boehringer Ingelheim Pharmceuticals, Inc., Ridgefield, Connecticut).
¶Except for ZDV chemoprophylaxis administered to HIV-exposed infants during the first 6 weeks of life to prevent perinatal HIV transmission; if an infant is identified as HIV-infected while receiving ZDV chemoprophylaxis, therapy should be changed to a combination antiretroviral drug regimen.

to take the drug. Intensive follow-up is required particularly during the critical first few months after therapy is started, with frequent patient visits to assess adherence, drug tolerance, and virologic response. Continued follow-up is needed to assess and reinforce adherence to the drug regimen.

2. Toxicities of antiretroviral drugs may occur at different frequencies in children and adults, and the implications of some of the toxicities for children are significantly different from adults. All efforts should be made to continue therapy in the presence of non-life-threatening toxicities. This should include liberal use of adjunctive measures such as granulocyte colony stimulating factor for treatment of neutropenia and erythropoietin and/or transfusions for treatment of anemia. If antiretroviral therapy must be discontinued for an extended period of time, to minimize the risk for developing drug resistance, all antiretroviral agents should be stopped simultaneously rather than continuing one or two agents alone because of potential increased viral replication.
3. Administering poorly palatable liquid antiretroviral formulations to children may be problematic. Innovative techniques to increase palatability may be needed to enable tolerance of medications.

Conclusion

While the general principles of therapy are the same for HIV-infected adults, adolescents, children and infants, treatment of pediatric infection requires an understanding of the unique aspects of HIV infection in children. Clinical trials of antiretroviral agents in children and the development of drug formulations appropriate for administration to children have often been delayed until after clinical trials in infected adults have been completed and/or the drug has been approved for use among infected adults. However, the paucity of pediatric-specific data cannot further deter the development of rational and reasonable pediatric treatment guidelines while studies in children are being undertaken. To maximize therapeutic options for HIV-infected pediatric patients throughout the course of their infection, drug formularies should facilitate the use of all FDA-approved antiretroviral agents as treatment options for children. Additionally, conducting clinical trials to define the pharmacokinetics, safety and effectiveness in ameliorating the pediatric-specific manifestations of HIV infection of current and new antiretroviral agents should be a priority. Studies of new drugs should be conducted coincident with or soon after initial studies have been completed in adults. The Working Group will revise these guidelines as new data on antiretroviral therapy for infected infants, children, and adolescents become available.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, June 1998						Total Cases Reported Statewide, January through June		
	State	Regions					This Year	Last Year	5 Yr Avg
		NW	N	SW	C	E			
AIDS	89	11	18	9	34	17	431	595	684
Campylobacteriosis	70	10	19	10	14	17	263	222	249
Giardiasis	26	3	7	4	4	8	167	204	134
Gonorrhea	487	30	38	59	143	217	2916	3976	5161
Hepatitis A	11	2	6	2	0	1	126	99	82
Hepatitis B	8	1	1	3	0	3	53	63	63
Hepatitis NANB	2	1	0	1	0	0	5	11	12
HIV Infection	83	3	16	3	32	29	450	477	421
Influenza	0	0	0	0	0	0	1034	438	626
Legionellosis	3	1	0	2	0	0	7	11	7
Lyme Disease	10	3	1	0	2	4	20	4	16
Measles	0	0	0	0	0	0	2	0	1
Meningitis, Aseptic	15	3	3	2	1	6	61	83	81
Meningitis, Bacterial†	3	0	0	1	0	2	29	44	49
Meningococcal Infections	3	1	2	0	0	0	23	35	34
Mumps	0	0	0	0	0	0	4	6	13
Pertussis	0	0	0	0	0	0	6	25	16
Rabies in Animals	69	20	14	15	7	13	330	304	232
Rocky Mountain Spotted Fever	2	2	0	0	0	0	2	4	3
Rubella	0	0	0	0	0	0	0	1	1
Salmonellosis	86	5	24	8	34	15	388	367	390
Shigellosis	12	0	2	0	1	9	66	256	227
Syphilis, Early‡	49	1	3	14	8	23	238	344	559
Tuberculosis	21	1	15	4	0	1	144	165	173

Localities Reporting Animal Rabies This Month: Accomack 1 raccoon; Albemarle 1 fox; Amelia 1 raccoon; Appomattox 2 skunks; Arlington 1 raccoon; Augusta 1 skunk; Bedford 2 raccoons; Campbell 1 raccoon; Chesapeake 2 foxes, 2 raccoons; Clarke 1 raccoon; Dinwiddie 1 raccoon; Fairfax 2 bats, 1 fox, 2 raccoons, 1 skunk; Fauquier 2 raccoons; Floyd 1 raccoon; Frederick 1 cat; Grayson 1 fox; Halifax 1 raccoon; King & Queen 1 cat; King George 1 skunk; Loudoun 1 fox, 1 raccoon; Louisa 2 raccoons; Lynchburg 1 fox; Mathews 1 groundhog; New Kent 1 fox, 1 raccoon; Northampton 1 raccoon; Orange 1 cat; Page 1 raccoon; Pittsylvania 2 raccoons; Prince Edward 1 raccoon; Prince George 1 raccoon; Prince William 1 bat, 1 opossum, 3 raccoons; Pulaski 1 bat; Rockbridge 1 cat, 1 skunk; Shenandoah 2 raccoons; Smyth 1 raccoon, 1 skunk; Southampton 1 raccoon; Spotsylvania 1 cat, 1 raccoon; Stafford 2 raccoons; Virginia Beach 1 bat, 3 raccoons; Warren 1 raccoon; Washington 1 raccoon; Wythe 1 raccoon.

Occupational Illnesses: Asbestosis 62; Carpal Tunnel Syndrome 41; Hearing Loss 17; Mercury exposure 1; Pneumoconiosis 7.

*Data for 1998 are provisional. †Other than meningococcal. ‡Includes primary, secondary, and early latent.

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