Viral load and CD4 testing in human immunodeficiency virus infection

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Policy contains: Acquired immune deficiency syndrome; CD4 count; drug resistance; HIV; human immunodeficiency virus; immunosuppression; viral load.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Plasma ribonucleic acid viral load testing (viral load) in adolescents and adults who have tested positive for human immunodeficiency virus type 1 is clinically proven and, therefore, medically necessary for any of the following indications (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019):

- Upon diagnosis.
- After first initiating antiretroviral treatment, within the first two to four weeks, and every four to eight weeks thereafter until the virus is undetectable.
- During the first two years of stable antiretroviral treatment, with no new human immunodeficiency virus-related symptoms, every three to four months.
- After two years of stable antiretroviral treatment, if the CD4 count is greater than 300 cells/mm^3, viral load testing may be extended to every six months.
- After changing antiretroviral regimens due to side effects or to change to a simpler (easier to manage) regimen, in a person with suppressed virus, measure after four to eight weeks to confirm efficacy of the new regimen.
- After changing antiretroviral regimens due to treatment failure (indicated by increased viral load), within the first two to four weeks, and every four to eight weeks thereafter until the virus is undetectable.

- While on antiretroviral treatment, if the viral load is consistently greater than or equal to 200 copies/mL, every three months.
- If member develops new human immunodeficiency virus-related symptoms, or initiates immunosuppressive treatment (e.g., with interferon, corticosteroids, or chemotherapy for cancer), every three months.

CD4 T lymphocyte count (also known as CD4, T4, or T-helper cells) testing in adolescents and adults who have tested positive for human immunodeficiency virus and are currently taking an antiretroviral regimen is clinically proven and, therefore, medically necessary for any of the following indications (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019):

- Upon diagnosis.
- After initiating antiretroviral therapy, at three months after initiation.
- During the first two years of stable antiretroviral treatment, with no new human immunodeficiency virus-related symptoms, every three to six months.
- After two years of being on stable antiretroviral therapy, if the viral load is undetectable, or after changing antiretroviral regimens due to side effects or to streamline the antiretroviral regimen, in members with suppressed virus, either:
    - If recent CD4 count is greater than or equal to 300 cells/mm^3, annually.
    - If recent CD4 count is greater than or equal to 500 cells/mm^3, optionally, not more frequently than annually.
- After changing antiretroviral regimens due to treatment failure (indicated by increased viral load), every three to six months.
- While on antiretroviral treatment, if the viral load is consistently greater than or equal to 200 copies/mL, every three to six months.
- If member develops new human immunodeficiency virus-related symptoms, or initiates immunosuppressive treatment (e.g., with interferon, corticosteroids, or chemotherapy for cancer), measure CD4 count and monitor according to new human immunodeficiency virus symptoms or opportunistic infections.

Viral load testing in children up to and including adolescents with sexual maturity rating (previously known as Tanner rating) I to III, who have tested positive for human immunodeficiency virus, is clinically proven and, therefore, medically necessary for any of the following indications (Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, 2020):

- Upon diagnosis.
- If a child has not begun antiretroviral therapy, the viral load should be monitored at least every three to four months.
- After initiating or changing an antiretroviral treatment regimen, at two to four weeks after initiation to monitor efficacy and adherence. Thereafter, viral load testing is recommended every three to four months to monitor continued adherence and disease progression.
- In children taking antiretroviral therapy, in the event of suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value, the viral load should be measured.

CD4 T lymphocyte count (also known as CD4, T4, or T-helper cells) testing in children living with human immunodeficiency virus, up to and including adolescents with sexual maturity rating (previously known as Tanner rating) I to III, to be medically necessary for any of the following indications (Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, 2020):

- Upon diagnosis.

- In children younger than 5 years, the CD4 percentage is recommended as an alternative to absolute CD4 counts.
- If a child has not begun antiretroviral therapy, the CD4 count should be monitored at least every three to four months.
- In children taking antiretroviral therapy, in the event of suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value, the CD4 count should be measured.
- In children and youth who are adherent to antiretroviral therapy, have sustained viral suppression and stable clinical status for two years or more, and have CD4 counts well above the level of risk for opportunistic infection (greater than or equal to 200 copies/mL), CD4 count can be measured every six to 12 months.

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations

The care of members with human immunodeficiency virus infection should be managed by an infectious disease specialist or other clinician qualified to care for patients with human immunodeficiency virus infection.

Upon testing positive for human immunodeficiency virus, all adolescents and adults should be tested for genotypic resistance and should begin taking an individually tailored antiretroviral regimen to delay clinical progression to advanced disease.

Resistance testing should be repeated when determining reasons for treatment failure and planning new regimens.

All members living with human immunodeficiency virus should be provided with treatment adherence education (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019).

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Measurement of CD4 cells and human immunodeficiency virus viral load has been used for decades to monitor human immunodeficiency virus disease progression and response to therapy (Kagan, 2015). CD4 count is a measure of immune system function. In a healthy person, the level of CD4 cells ranges from 500 to 1500 cells/mm^3, and averages approximately 800 cells/mm^3. In human immunodeficiency virus infection, the virus replicates and attacks and kills the CD4 cells, depleting them and thereby damaging the immune system. Without effective treatment, the CD4 cells eventually decrease to a level which leaves an individual vulnerable to many possible infections and associated conditions.

A diagnosis of progression to acquired immune deficiency syndrome is made based on either of the following criteria: the CD4 cells fall to 200/mm^3 or below, or the individual is diagnosed with one or more of several different opportunistic infections or associated conditions. In an individual with human immunodeficiency virus infection and depleted CD4 cells who initiates effective antiretroviral treatment, the CD4 cells generally slowly increase. Measurement of CD4 cells is particularly important before starting antiretroviral treatment. Because most people living with human immunodeficiency virus/acquired immune deficiency syndrome are taking antiretroviral treatment, the rationale for frequently measuring CD4 cells has lessened.

In contrast, the measure of viral ribonucleic acid load varies according to the response to antiviral medication (Athe, 2015). The natural history of untreated human immunodeficiency virus is for the viral load to rise upon

infection, decrease for a variable period during which time the individual may infect sexual partners and those in contact with bodily fluids, and then begin to rise again. The ascent of the viral load and the continual attack on the immune system can be suppressed through treatment with highly active antiretroviral medication. There are currently several classes of antiretroviral medications, each of which is designed to intervene at a different point in the human immunodeficiency virus life cycle, and multiple drugs must be taken simultaneously to be effective.

Determination of the optimal combination of drugs to both suppress the virus and prevent development of viral resistance to medication is made based on results of genotypic resistance testing. The response to treatment is assessed through retesting of the viral load. Point-of-care viral load tests are in development but not yet available (Estill, 2015).

Findings

The value of frequently monitoring CD4 counts has lessened as the ability to directly measure viral load has increased and as antiretroviral treatment has become more effective. The World Health Organization (2013) recommended viral load monitoring as the optimal method of monitoring response to antiretroviral treatment. The U.S. Department of Health and Human Services has issued antiretroviral treatment and monitoring guidelines for pediatric, adolescent, and adult populations (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2014 [included within 2018 publication]; Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, 2018). This summary focuses on data collected in the United States and Europe.

Results from the AntiRetroviral Therapy with TMC114 Examined in Naïve Subjects (ARTEMIS) trial, which randomized 689 treatment-naïve participants to either of two arms of different antiretroviral treatments, showed a benefit to measuring CD4 cells in the first 48 weeks of treatment (Girard, 2013). After 48 weeks of treatment, among those participants whose virus had responded (viral load having fallen to less than 50 copies/mL and CD4 count having risen to greater than or equal to 200/mm^3), there appeared to be little benefit to continual CD4 monitoring. Among the 449 participants whose viral load was sustained at less than or equal to 400 copies/mL over weeks 49 to 192, only five participants (1.1%) experienced CD4 decreases below 200 cells/mm^3 in the same period, all of which were transient decreases with follow-up measures all showing CD4 greater than or equal to 200 cells/mm^3.

A regression tree analysis was used to carry out 1,000 repeats of a model using randomly selected observations in children (Group I) and adolescents and adults (Group II) (Guar, 2013). The analysis resulted in a correct predictive ability of 89.6% (standard error 2.3%) in Group I and 95.6% (standard error 1%) in Group II. The authors concluded that the results provided a classification tree to determine whether the CD4 count is currently above or below the age-specific cutoff for prophylaxis for Pneumocystis carinii pneumonia, now known as Pneumocystis jovereci pneumonia (Stringer, 2002), that would allow less frequent CD4 testing.

A meta-analysis of 13 studies (12 published and one unpublished) including 20,297 participants found a pooled proportion of 0.4% (95% confidence interval, 0.2% to 0.6%) who experienced an unexplained and confirmed decline in CD4 count in the context of viral suppression (Ford, 2015). None of the included studies described adverse clinical events among those whose CD4 cell counts declined. The authors concluded that these findings support “reducing or stopping” routine CD4 monitoring among those who maintain viral suppression on antiretroviral therapy.

An analysis of CD4 testing trends based on a previous version of the guidelines in 28,530 veterans living with human immunodeficiency virus/acquired immune deficiency syndrome found that, based on their most recent CD4 test and length of stable viral suppression, 19.8% were eligible for optional monitoring and 15.6% were eligible for minimal monitoring (Barnett, 2016). CD4 testing in this sample declined by 10.8% over a period of four years. The authors suggested that full implementation of the 2014 guideline could reduce CD4 testing a further 28.9%, and concluded that reduced CD4 monitoring based on the schedule promoted in the 2014

guidelines would result in modest cost savings and “likely” reduce patient anxiety associated with frequent monitoring, while resulting in little or no impact on the quality of care.

An analysis of the probability of decreasing CD4 cells (less than 350 cells/mm^3) in participants at two sites in Genoa, Italy, found a probability of more than 98.0% that those who are stable on antiretroviral therapy would maintain an elevated CD4 count (DiBiagio, 2017). Coinfection with hepatitis C virus and a previous viral load of more than 50 were associated with CD4 cells decreasing below 350 cells/mm^3. A model forecasting reductions in testing to once annually for stable patients without hepatitis C coinfection, and twice annually in those with hepatitis C coinfection, resulted in an estimated cost savings of 50% in CD4 testing.

Reflecting the trend in the above findings, updated guidelines from the World Health Organization (2016) suggest that CD4 monitoring can be stopped in those with stably suppressed virus, in settings where viral load monitoring is available. Guidelines from the Department of Health and Human Services (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2014; Panel on Antiretroviral Guidelines for Children, 2018) support decreasing the frequency of CD4 monitoring in those who maintain viral suppression while on antiretroviral therapy.

Clinical management of those with persistently low CD4 counts

Both morbidity and mortality are elevated in individuals with suppressed viral loads but persistently low CD4 counts or persistent immune activation or inflammation. There are no interventions known to be effective in raising CD4 cell counts or to reduce the associated immune system activation or inflammation. It is not recommended to attempt to increase the CD4 count by adding an agent to an antiretroviral regimen that is effectively suppressing the virus. The most recent guidelines published by the Department of Health and Human Services (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2018) recommend that in cases of poor CD4 recovery, clinical efforts should focus on modifiable behaviors such as reducing chronic disease factors (smoking cessation, healthy nutrition, exercise, and treatment of hypercholesterolemia and hyperlipidemia).

In 2021, we updated the guidelines by the Panel on Antiretroviral Guidelines for Adults and Adolescents (2019, update of 2018) and the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (2020, update of 2019). No policy changes are warranted.

References

On April 27, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “CD4,” “human immunodeficiency virus,” “HIV,” “monitoring,” and “viral load.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

5/2019: initial review date and clinical policy effective date: 6/2019

2/2020: Policy references updated.

7/2021: Policy references updated.