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Hepatitis C infection in Alaska Natives with persistently normal, persistently elevated or fluctuating alanine aminotransferase levels

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Abstract: *Background/Aims:* An estimated one-third of patients with chronic hepatitis C virus (HCV) infection have persistently normal alanine transaminase (PNALT); however, in many previous studies alanine aminotransferase (ALT) levels were followed for ≤ 12 months.

Methods: We analyzed data from a population-based cohort of 935 Alaska Natives with HCV, recruited from 1994 to 2005, to determine the proportion of persons with PNALT, persistently elevated ALT (PEALT), and fluctuating ALT (FLUXALT) to determine factors for each ALT state. We selected persons with two positive HCV RNA results ≥ 1 year apart and ≥ 6 ALT levels measured over the subsequent 3 years with at least 1 month between ALT measurements ($n = 265$). We defined a person as having PNALT, PEALT, or FLUXALT when all six ALT levels were normal, elevated, or did not fit either of the above two categories, respectively, during the 3-year follow-up period. *Results:* Among 208 persistently HCV RNA-positive persons, 13 had PNALT, 121 PEALT, 74 FLUXALT. Among 77 persons who underwent liver biopsy, those with PEALT were more likely to have Ishak fibrosis scores > 2 compared with persons with FLUXALT (44% vs. 10%, OR 7.0, 95% CI: 1.5–33.2). No statistically significant differences were found in ALT classification by age, gender, infection duration, median body mass index, alcohol consumption, residence, risk behavior, RNA level, or genotype. *Conclusions:* Only 6% of persons with chronic HCV had PNALT. Persons with PEALT were significantly more likely to have higher fibrosis scores on liver biopsy than those with FLUXALT. Previous studies with short follow-up periods may have overestimated the proportion of persons with normal ALT levels.

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Hepatitis C virus (HCV) is a significant cause of chronic liver disease in the United States where an estimated 2.7 million persons have chronic infection (1). It has been estimated that approximately one-third of patients with chronic HCV infection have persistently normal alanine transaminase (PNALT) levels (2–9). The 2002 National Institutes of Health Consensus Conference on HCV concluded that the benefits of treatment of HCV-infected patients with normal serum alanine aminotransferase (ALT) levels was of uncertain value and should not be undertaken routinely; however, at that time they did not define what constitutes a ‘normal’ ALT level (10). Over the

past decade, several studies using differing definitions of PNALT have been performed to characterize HCV-infected persons with PNALT and compare them with HCV-infected persons with elevated ALT levels; the results of these studies have varied widely. Most investigators have defined PNALT as ≥ 3 normal ALT measurements over a 6–12-month period of time in persons infected with HCV. In these studies, the number of measurements was small, and the time duration was sufficiently short that many patients with fluctuating ALT (FLUXALT) levels could have been misclassified as having PNALT (4, 5, 11–13).

Recently, inadequacies of the currently accepted definition of PNALT have been recognized and new definitions using a substantially longer duration of follow-up and a greater number of ALT measurements have been recommended (9, 14–16). Since 1996, we have conducted a comprehensive study of HCV in the Alaska Native population, allowing us to examine the relationship between chronic hepatitis C and ALT levels. The aims of this study were: (1) to correlate mean ALT level with polymerase chain reaction (PCR) status and HCV RNA level, (2) to redefine the terms PNALT, persistently elevated alanine aminotransferase (PEALT), and FLUXALT using a longer duration of follow-up, and a greater number of ALT measurements, and (3) to compare clinical, demographic, and risk factor data as well as viral load and genotype between persons with PNALT, PEALT, and FLUXALT.

Materials and methods

HCV registry and long-term outcome study

In 1992, the Alaska Native Medical Center (ANMC) Viral Hepatitis Program began a registry of Alaska Natives with hepatitis C to improve patient care and tracking. The ANMC medical laboratory provides free testing for anti-HCV to all hospitals and clinics in the state of Alaska who serve Alaska Natives. All persons positive for anti-HCV performed by enzyme-linked immunosorbent assay (ELISA), and confirmed by a positive recombinant immunoblot assay (RIBA) or HCV RNA assay were enrolled in this registry. In addition, each year any Alaska Native person who tests positive for anti-HCV and is reported to the State of Alaska is included in this registry. In 1994, a study of hepatitis C outcomes was begun by recruiting patients from this registry into a long-term outcome study. Upon enrollment, a patient medical history, physical examination, and laboratory evaluations were performed on each participant. Participants completed an in-person standard interview administered by a study nurse to obtain demographic data and information about risk factors and behaviors associated with HCV infection (17). Participants who met criteria outlined in recent HCV Practice Guidelines were offered antiviral therapy (10, 18). A detailed description of this registry has been previously reported (17).

Laboratory testing

ALT testing was performed at the ANMC laboratory on an Abbott Aeroset machine using

Abbott laboratory reagents (Abbott Laboratories, Abbott Park, IL). A normal ALT level was defined as <40 U/l. Testing for anti-HCV was performed by ELISA using commercial assays (HCV 2.0; Abbott Laboratories, Abbott Park, IL). Persons with an anti-HCV antibody-positive specimen had further testing by RIBA (Chiron Corporation, Emeryville, CA) or PCR. Testing for HCV RNA and HCV genotype was performed at the University of Washington. HCV viral RNA levels were determined by the branched DNA assay (bDNA) version 2.0 (Bayer Corporation, Tarrytown, NY) and by quantitative reverse transcription-polymerase chain reaction (RT-PCR). The limit of detection of the bDNA assay was 200 000 genome equivalents/ml (g equivalents/ml). These results were converted to international units (IU/ml) using the manufacturer's recommended conversion factor of 5.8 g equivalents/ml to 1 IU/ml. For samples negative below this limit, an endpoint dilution assay using Roche Amplicor (Roche Diagnostic Systems, Branchburg, NY) was used to further characterize low-level viremia (limit 100 copies/ml). HCV genotype was performed by restriction fragment length polymorphism analysis of the 5' non-coding region as described previously (19).

All participants were tested for antibody to hepatitis B core antigen (anti-HBc). Those with a positive anti-HBc were also tested for hepatitis B surface antigen (HBsAg), and antibody to HBsAg (Corzyme, Auszyme monoclonal, and Ausab ELISA, Abbott Laboratories, Abbott, IL). Persons positive for HBsAg, human immunodeficiency virus, and those treated for HCV infection during the 3-year follow-up period were excluded from the analysis. Liver biopsies were reviewed by the study pathologist who was blinded to the clinical information. Biopsies were scored for inflammation using the Hepatic Activity Index of Knodell and for fibrosis using the Knodell scoring system and the modified scoring system of Ishak.

IRB approval and informed consent

The study was approved by the Alaska Area Native Health Services Institutional Review Board (IRB), the Indian Health Service National IRB, and the Centers for Disease Control and Prevention IRB. In addition, three regional Alaska Native health boards approved the study. All participants gave written informed consent.

Study participants ($n = 265$)

We sought to redefine PNALT, PEALT, and FLUXALT using more stringent criteria than

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those used in previous studies, and therefore selected only those Alaska Native persons who had six or more ALT measurements available, occurring a minimum of 1 month apart during the first 3 years of follow-up. Additionally, we required a minimum of two HCV RNA determinations in the 3 years after consent. The first HCV RNA result was determined within 1 year of consent date and we required that the second HCV RNA result be determined within 1 year of the end of the 3-year follow-up period. During the 3-year follow-up period, persons were classified as having PNALT if all six ALT levels were normal (<40 U/l), PEALT if all six ALT levels were elevated (>40 U/l), or FLUXALT for persons who did not fit into either of the above two categories. In persons with >6 ALT determinations, we used the six ALT tests that were measured at or closest to a 6-month time interval (at 0, 6, 12, 18, 24, and 30 months) for categorizing persons as PNALT, PEALT, or FLUXALT. We selected persons with positive HCV RNA results ($n=208$) and compared them across ALT categories by demographic, viral characteristics (genotype and quantitative RNA), and fibrosis score.

Statistical analysis

Statistical analysis was completed using SAS (version 8.0, SAS Institute, Cary, NC) and Epi Info (version 6.04b, Centers for Disease Control and Prevention, Atlanta, GA). The Cochran–Armitage test of trend was used to compare the proportion of persons that were HCV RNA-positive and persons with an RNA concentration level $\geq 1 \times 10^6$ IU/ml by median ALT.

For comparisons between the new ALT classifications (PNALT, FLUXALT, and PEALT), we used the Kruskal–Wallis test and χ^2 test for comparison of continuous and categorical variables, respectively. *P*-values are exact when appropriate and two-sided; a value <0.05 was considered statistically significant.

Results

Descriptive epidemiology

Between January 1, 1994 and June 30, 2005, 935 Alaska Natives were enrolled in the long-term HCV outcome study. Demographic characteristics of persons enrolled in the hepatitis C outcome study ($n=935$), and this ALT substudy ($n=265$) are shown in Table 1. When compared with persons in the long-term HCV outcome study, substudy participants did not differ significantly by age, sex, residence, median body mass index,

Table 1. Comparison of characteristics of Alaska Native hepatitis C cohort ($n=935$) to participants in ALT sub-study ($n=265$)

| Characteristic | Hepatitis C outcome study ($n=935$) | Sub-study ($n=265$) |
|--|---------------------------------------|-----------------------|
| Sex (% female) | 53% (500) | 55% (147) |
| Mean age at consent (years) | 41.5 | 42.5 |
| Urban vs. rural (% urban) | 66% (616) | 70% (187) |
| Risk factor | | |
| IVDU | 61% (573) | 55% (155) |
| BT | 14% (134) | 18% (48) |
| Other | 24% (228) | 23% (62) |
| Median body mass index | 27.4 | 27.2 |
| History of heavy ETOH use* | 32% (298) | 36% (95) |
| Current heavy ETOH use† | 14% (133) | 16% (42) |
| Estimated length of HCV infection (years) | 13.9 | 14.5 |
| Age at estimated year of infection (years) | 27.5 | 27.8 |
| RNA-positive persons | ($n=673$ ‡) | ($n=208$) |
| Genotype | | |
| 1 | 63% (421) | 62% (129) |
| 2 | 22% (149) | 22% (46) |
| 3 | 15% (97) | 16% (33) |
| 4 | 0.1% (1) | 0% (0) |
| Median ALT level at Consent | 69.0 | 79.0 |
| % with normal ALT at Consent | 19% (131/673) | 15% (32/208) |

*Self-reported ever having consumed >50 g/day of alcohol. †Self-reported >50 g/day of alcohol consumption at the start of follow-up. ‡Genotype not available from five persons. ALT, alanine aminotransferase.

alcohol (ETOH) consumption history, estimated length of HCV infection, ALT level at time of consent, or HCV genotype. The percentage of HCV RNA-positive persons with a normal ALT level (<40 U/L) at the time of consent into the study were similar (Table 1) between the two groups. Among the 673 HCV RNA-positive persons in the long-term HCV outcome study with an ALT measurement at the time of consent, 131 (19%) had normal ALT levels. Of the persons with a normal ALT at consent, 52% (66/128) had ≥ 1 elevated ALT level in the following 3 years (three persons were lost to follow-up). The previous results were similar when persons who reported current heavy alcohol consumption were removed from the analysis (20% with normal ALT levels at consent, 49% of whom had ≥ 1 elevated ALT during the 3-year follow-up period).

Sub-study results ($n=265$)

The percentage of persons that were HCV RNA-positive increased along with the median ALT level ($P<0.01$, Table 2). No relationship was detected between median ALT level and HCV RNA viremia level among PCR-positive persons (Table 2). Of the 265 with ≥ 6 ALT measurements available during the follow-up period; 208 (79%) were HCV RNA-positive. Among those persons who were persistently HCV RNA-positive,

Table 2. The proportion of participants who are RNA-positive grouped by their median ALT level of all measurements taken in 3 years after consent

| Median ALT level | % RNA-positive (n = 265) | Among PCR-positive persons (n = 208) | |
|-------------------|--------------------------|---|-----------------------|
| | | Median viremia level (in thousands IU/ml) | % ≥ 1 million (IU/ml) |
| 0–28 | 28% (11/39) | 485 | 36% (4/11) |
| 29–40 | 66% (21/32)* | 885 | 43% (9/21) |
| 41–56 | 82% (36/44)* | 629 | 42% (15/36) |
| 57–80 | 88% (43/49) | 346 | 33% (14/43) |
| 81–120 | 93% (55/59) | 585 | 36% (20/55) |
| ≥ 120 | 100% (42/42) | 415 | 38% (16/42) |
| P-value for trend | <0.01 | 0.33 | 0.73 |

*P-value for % RNA-positive between median ALT level 29–40 vs. 41–56 was 0.11. All participants had at least 2 RNA results to determine if they were PCR-positive or negative (total n = 265). ALT, alanine aminotransferase; PCR, polymerase chain reaction.

13 (6%) had PNALT, 74 (36%) had FLUXALT, and 121 (58%) had PEALT. After removal of persons who reported current heavy ETOH consumption, 12 (7%) had PNALT, 63 (36%) had FLUXALT, and 100 (57%) had PEALT. Of the 57 persons who were persistently HCV RNA-negative, 23 (40%) had PNALT, 29 (51%) had FLUXALT, and 5 (9%) had PEALT. Persons who were persistently HCV RNA-positive were more likely than those who were persistently negative to have PEALT (58% vs. 9%, respectively; $P < 0.001$).

Among the 13 persons who were HCV RNA-positive and had PNALT, the distribution of their

ALT determinations was relatively evenly spread throughout the normal range with 31% at <50% of the upper limit of the normal (ULN) range for ALT, 41% between 50 and 75%, and 28% between 75 and 100% of the ULN range. Of the 121 persons with PEALT, 90% of the ALT determinations were ≥ 1.5 times the ULN range. (Fig. 1)

Demographics, risk factors, and HCV genotype by new ALT category

No differences were found by age, gender, residence, median body mass index, estimated length of HCV infection, alcohol usage, and HCV genotype in RNA-positive persons who had PNALT, FLUXALT, or PEALT. The low sample size of persons with PNALT (n = 13) limited the power to detect differences in characteristics between persons with PNALT and the other two groups. Among persons with PNALT, 62% were female, 31% reported a history of alcohol use, and 54% had >1 × 10⁶ HCV RNA IU/ml (Table 3).

Fibrosis by ALT category

Liver biopsies were performed on 1, 20, and 57 individuals with PNALT, FLUXALT, and PEALT, respectively. Persons with PEALT were more likely to have an Ishak fibrosis score >2 when compared with persons with FLUXALT (44% vs. 10%, OR = 7.0, 95% CI: 1.5–33.2, P = 0.003) or a Knodell fibrosis score >1 (37% vs. 5%, OR = 11.1, 95% CI: 1.4–88.9, P = 0.002). Individuals with PEALT were also more likely to have a Hepatic

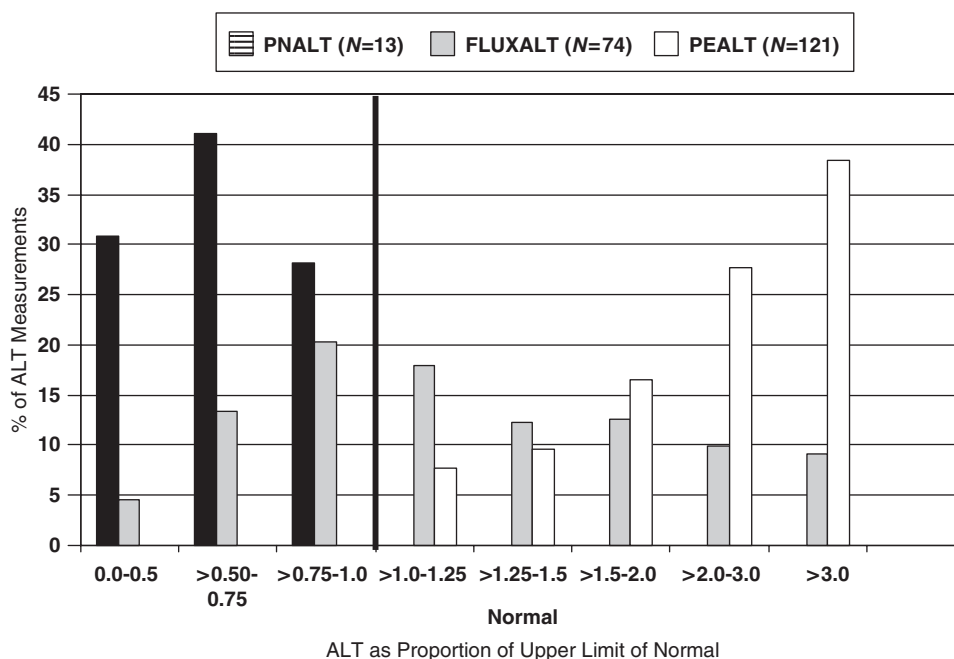


Fig. 1. Distribution of alanine aminotransferase levels by category among hepatitis C virus RNA-positive persons (n = 208).

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Table 3. Comparisons of demographic and viral characteristics among RNA-positive persons who had persistently normal (PNALT), fluctuating (FLUXALT), and persistently elevated (PEALT) ALT levels

| Characteristic | PNALT <i>n</i> (%) (<i>n</i> = 13) | FLUXALT <i>n</i> (%) (<i>n</i> = 74) | PEALT <i>n</i> (%) (<i>n</i> = 121) | <i>P</i> -value* |
|---|--|--|---|------------------|
| Sex (% female) | 62% (8) | 55% (41) | 45% (54) | 0.23 |
| Mean age at consent (years) | 41.0 | 42.8 | 43.1 | 0.86 |
| Urban vs. rural (% urban) | 62% (8) | 76% (56) | 69% (83) | 0.43 |
| Risk factor | | | | |
| IVDU | 69% (9) | 50% (37) | 62% (75) | |
| BT | 8% (1) | 23% (17) | 18% (22) | 0.38 |
| Other | 23% (3) | 27% (20) | 20% (24) | |
| Median Body Mass Index | 26.0 | 27.8 | 28.0 | 0.10 |
| History of heavy ETOH use† | 31% (4) | 36% (27) | 38% (46) | 0.87 |
| Current heavy ETOH use‡ | 8% (1) | 15% (11) | 17% (21) | 0.60 |
| Estimated length of HCV infection (years) | 15.1 | 14.9 | 15.9 | 0.65 |
| Age at estimated year of infection | 26.3 | 28.1 | 27.3 | 0.56 |
| Genotype | | | | |
| 1 | 46% (6) | 66% (49) | 61% (74) | |
| 2 | 46% (6) | 16% (12) | 23% (28) | 0.24 |
| 3 | 8% (1) | 18% (13) | 16% (19) | |
| RNA > 1 × 10 ⁶ § | 54% (7) | 34% (25) | 38% (46) | 0.39 |

*Comparing across all three ALT categories (Kruskal–Wallis test and χ^2 test used for continuous and categorical variables, respectively) †Self-reported ever having consumed > 50 g/day of alcohol. ‡Self-reported > 50 g/day of alcohol consumption at the start of follow-up. §At the start of the 3-year follow-up period in IU/ml. ALT, alanine aminotransferase.

Activity Index (HAI) score >9 compared with persons having FLUXALT (42% vs. 5%, OR = 13.8, 95% CI: 1.7–110.4, $P = 0.0007$). HAI and fibrosis scores in persons with PNALT were not analyzed because only one person with PNALT had a liver biopsy.

Discussion

We examined a population-based cohort of Alaska Natives with hepatitis C and determined that only 6% of Alaska Natives with chronic HCV infection had PNALT, suggesting that previous studies, which reported that 25–30% of persons with HCV had PNALT, may have overestimated the proportion of HCV-infected persons with PNALT (8, 20, 21) by inadvertently including persons with FLUXALT. This study is unique in its use of a minimum of six ALT measurements taken more than 1 month apart over at least a 3-year period. Of the 13 patients who fulfilled the criteria we defined for PNALT, seven had one or two additional ALT determinations performed and each of those results were also normal. By using a greater number of ALT measurements and longer time duration than has previously been done, we were able to determine that 36% of persons with chronic HCV had fluctuating ALT levels. Less stringent definitions of PNALT, FLUXALT, and PEALT that have been used (shorter timeframe and fewer measurements) may result in patients with fluctuating ALT levels being misclassified. Overestimation of the percentage of persons with PNALT may

lead to erroneous conclusions about this group of HCV infected persons. For instance, providers and patients may assume that if ALT levels are repeatedly normal over a short period of time such as 3–6 months, regular follow-up is not important. In addition, patients initially thought to have PNALT who, on longer follow-up, experience FLUXALT levels may be at risk of fibrosis progression and could be good candidates for antiviral treatment.

In this study, we found that HCV RNA-positive Alaska Natives with PEALT had significantly more fibrosis and inflammation on biopsy when compared with persons having FLUXALT. This suggests that persons with persistently elevated ALT levels may have a more rapid progression of fibrosis than those with fluctuating ALT levels; however, this remains to be confirmed by a study in which serial biopsies are performed. Differences in HCV RNA-positive persons with fluctuating or persistently elevated ALT levels have not been previously reported on.

Some studies suggest that 17–25% of HCV-infected persons with PNALT have moderate chronic hepatitis and 9–20% have moderate-to-severe fibrosis (5, 11, 12, 22, 23) while other studies found that persons with PNALT had more indolent disease with the majority having mild fibrosis on biopsy and a slower progression of liver disease (16, 24–28). The discrepancies in previous study findings could be due to the different definitions of PNALT that were used. It is likely that in numerous studies, persons who truly had FLUXALT were misclassified as having PNALT, leading to an

overestimate of the risk of moderate to severe fibrosis in persons with PNALT. However, since only one of our patients with PNALT had a liver biopsy, we were unable to clarify this.

In this study, we looked at the correlation between ALT levels and HCV status and found that the percentage of HCV RNA-positive persons increased along with the median ALT level. In addition, we found that HCV RNA-positive persons were more likely to have PEALT or FLUXALT than persons who were persistently HCV RNA-negative; however, we did not find an association between quantitative viremia level and ALT level, a finding supported by previous studies (23, 29). A more detailed study on correlates to HCV viremia level over time is ongoing within this cohort.

We found no significant predictors of ALT category by age, gender, estimated length of HCV infection, alcohol usage, risk factors (IV drug abuse, blood transfusion, etc.) or HCV genotype in HCV RNA-positive persons. Similar to previous studies, we found that a higher proportion of HCV-positive persons with PNALT were female (5, 23).

Our population-based study suggests that few patients with chronic HCV have persistently normal ALT levels. In fact 52% of patients positive for HCV RNA in our study, who had normal ALT levels at the time of consent, subsequently were found to have elevated ALT levels, and we found a smaller proportion of persons with persistently normal ALT levels than previous studies (2–8). However, we still may have overestimated the proportion of persons who have PNALT as the upper limit of normal for ALT in our laboratory during the period of this study was 40 IU/ml and this level may be too high. Recently, it has been suggested that the upper limit of the normal range of ALT levels used in most medical laboratories is set at an arbitrarily high level. A recent study that removed patients with risk factors for non-alcoholic fatty liver disease and other liver diseases from inclusion in calculations of the normal range of ALT has suggested that a level of <30 IU/ml for men and <20 IU/ml for women should be considered the upper end of the normal range (30). Using these cutoffs, we found that only one of 208 (0.5%) HCV RNA-positive persons in our study would fit these revised criteria for PNALT.

In our study, liver biopsy was available on only one person with PNALT. Liver biopsy is not a requirement to participate in our study; the decision to biopsy is left up to the physician providing care and to the patient. In addition, as liver biopsies are not routinely recommended for patients with normal ALT levels (10, 18), they were

not usually performed on persons with normal ALT levels in our study. This limitation has not allowed us to compare the liver pathology findings of those participants with PEALT and FLUXALT with those having PNALT. In addition, this study was not designed to determine how frequently ALT testing on HCV RNA-positive patients needs to be performed to reliably confirm PNALT. While the Liver Disease and Hepatitis Program at the ANMC recommends ALT levels be performed at least every 6 months in patients with chronic hepatitis C, ALT levels in this study were obtained when patients came to clinic, and at the physician's discretion; therefore we do not have data from all patients at set time points. Data from this study of Alaska Natives may not be generalizable to the US population, although we have shown that this study population has characteristics similar to those seen on other US populations of HCV-infected individuals (17).

In conclusion, the findings from our study suggest that infrequent or short-term monitoring of ALT in persons infected with HCV may lead to misclassifying patients as having PNALT when they really have FLUXALT. In fact, since only 6% of our cohort had persistently normal ALT levels, we can conclude that over time, most individuals whose ALT levels are normal on initial evaluation will be found to have ALT levels that will be above the upper limit of normal when followed at regular intervals and therefore might need to be evaluated with liver biopsy and considered for antiviral therapy. The currently used definition of PNALT (three normal ALT measurements over a 6-month period) does not reliably exclude FLUXALT and therefore consideration should be given to revising the definition of PNALT based on a longer timeframe and a greater number of ALT measurements.

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