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Longitudinal Changes in Liver Enzyme Levels Among Transgender People Receiving Gender Affirming Hormone Therapy

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SUPPLEMENTARY MATERIALS

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Abstract

Background: The effect of gender affirming hormone therapy (GAHT) on clinical laboratory parameters, including levels of liver enzymes alanine aminotransferase (ALT) and aspartate transaminase (AST), is an area of uncertainty in transgender health.

Aim: We sought to estimate the distribution parameters of liver enzyme levels among transmasculine (TM) and transfeminine (TF) persons receiving GAHT relative to the corresponding measures in cisgender reference groups, and to evaluate longitudinal changes in these laboratory measures following GAHT initiation.

Methods: The data for this longitudinal study included 624 TF and 438 transmasculine (TM) people as well as 4,090 cisgender males and 4,797 cisgender females enrolled in 3 integrated health systems. Time under observation was divided into 2 intervals: from the first blood test to the date of the first filled GAHT prescription and from GAHT initiation to the most recent ALT or AST measurement. Linear mixed models were used to compare changes in log-transformed ALT and AST values among transgender cohort members before and after GAHT initiation, and relative to the reference groups. The results were expressed as relative differences (in %) and the ratios of these differences (ratios-of-ratios) along with the 95% confidence intervals (CIs).

Outcomes: Changes in ALT and AST levels among transgender people over time and relative to the corresponding changes in cisgender referents.

Results: Among TM study participants, the post GAHT ratios-of-ratios for AST were 1.61 (95% CI: 1.13, 2.31) and 1.57 (95% CI: 1.06, 2.31) relative to cisgender males and females respectively. For ALT, the corresponding comparisons yielded the ratios-of-ratios (95% CIs) of 2.06 (1.67, 2.54) and 1.90 (1.50, 2.40). No statistically significant changes were observed among TF participants. Other factors associated with higher liver enzyme levels included alcohol use/abuse and obesity.

Clinical Implications: TM persons may experience modest increases in ALT and AST concentrations following testosterone initiation; however, clinical significance of the observed association remains unclear and requires further investigation. By contrast, feminizing GAHT is unlikely to induce appreciable changes in liver enzyme levels.

Strength and Limitations: The strengths of this study are the longitudinal design and the ability to assemble an unselected cohort nested within large health systems. The main limitations include the lack of information on hormone levels and the inability to take into account GAHT doses and routes of administration.

Conclusion: The influence of long-term GAHT on ALT and AST levels appears modest and not likely to reflect clinically meaningful changes in liver function.

Keywords

Gender Affirming Hormone Treatment; Liver Function Test; Liver Enzyme; Transgender Health

INTRODUCTION

Transgender people constitute a sizable and growing proportion of the US population.[1,2] Gender affirming hormone therapy (GAHT) is essential for improving well-being and quality of life of transgender people.[3–5] In transfeminine (TF) persons, GAHT usually includes estrogen along with testosterone lowering medications, while testosterone is the main hormone treatment for transmasculine (TM) individuals.[6,7]

Transgender health is an emerging field with a multitude of unmet data needs, and recent comprehensive reviews provide a long list of research priorities related to management of transgender patients.[8–13] One area of interest in transgender health research is the frequency and magnitude of GAHT-induced effects on clinical laboratory test results. The World Professional Association for Transgender Health and the Endocrine Society recommend monitoring a variety of laboratory parameters in transgender persons receiving GAHT.[14,15] These include markers of erythropoiesis, indicators of glucose metabolism, measures of renal function, as well levels of liver enzymes.[14]

Aminotransferases are a group of liver enzymes that catalyze the conversion of amino acids to α-ketoglutarate.[16–18] The reactants and products of this conversion are important for numerous cell functions including glucose regulation and electron transport.[16–18] The enzymes commonly used as markers of liver disease in clinical practice are alanine aminotransferase (ALT) and aspartate transaminase (AST). Whereas ALT is a specific indicator of liver function, AST concentration also increases in response to muscle injury.[17–18] The normal levels of serum ALT and AST may vary across laboratories, but are typically less than 40 IU/L.[16–18] ALT has longer half-life than AST, and in the presence of liver disease, its levels tend to be much higher than the levels of AST.[16]

GAHT is expected to affect levels of ALT and AST in transgender people because liver function is known to be regulated, at least in part, by circulating sex hormones.[16,17] In cisgender populations, women have slightly lower absolute levels of ALT and AST, but have higher AST/ALT ratios compared to men.[19,20] Estradiol may affect liver function through its action on estrogen receptor α, which acts as a coordinator of energy metabolism in the liver.[21,22] Estrogen fluctuation affects synthesis of fatty acids and cholesterol, which in turn may be linked to liver enzyme production and regulation.[23,24] In addition, low estrogen levels have been linked to increased risk of non-alcoholic fatty liver in both human and animal studies.[25–28] The effect of testosterone on liver function is less understood although it is known that liver contains androgen and estradiol receptors[16,28] and testosterone is converted to estradiol by aromatase in liver locally.[28–30] Both lack of testosterone in men with hypogonadism and excess of testosterone in women diagnosed with polycystic ovary syndrome increase the risk of non-alcoholic fatty liver disease, and therefore may result in abnormal levels of liver enzymes.[25,27–30]

Several studies have examined the relation between GAHT and levels of AST and ALT[31–43]; however, the evidence from these studies is somewhat limited due to the lack of comparison cisgender groups, small sample sizes and relatively short duration of follow up. With these considerations in mind, the overall goal of this project was to use data from a large, cohort

of transgender people to evaluate the relation between GAHT and changes in ALT and AST levels over time. Specifically, we sought to estimate the distribution parameters of liver enzyme levels among TM and TF persons receiving GAHT relative to the corresponding measures in cisgender reference groups, and to evaluate longitudinal changes in these laboratory measures following GAHT initiation.

METHODS

Cohort Ascertainment and Data Collection

The Institutional Review Boards at all participating sites reviewed and approved all study elements. The details of the study that provided data for the current analysis were described in previous publications.[44–46] Briefly, the Study of Transition, Outcomes and Gender (STRONG) aimed to examine health status of transgender people and to compare various measures of health status among transgender participants to those of cisgender reference cohorts. STRONG cohort members were identified from 2006 to 2014 from the electronic medical records of individuals enrolled in Kaiser Permanente (KP) health plans in Northern California, Southern California, and Georgia.

The current study focused on transgender participants in the hormone initiation group, which included individuals who started GAHT at KP after the index date (calendar year of the first recorded evidence of transgender status in KP). Each transgender cohort member was categorized as TF or TM. The TM and TF assignment methodology was described and validated previously.[44–46] The receipt of GAHT was ascertained based on filled hormone therapy prescription information documented in the pharmacy records. Each transgender subject was matched to 20 cisgender subjects (10 female and 10 male) only based on the calendar year of the first recorded evidence of transgender status (index date).

The transgender cohort members were eligible for analysis if they were at least 18 years of age at index date, and underwent at least one blood test both before and after the date of GAHT initiation. The dependent variables of interest included the 2 liver enzymes – ALT and AST. The transgender subjects were compared to cisgender males (CM) and cis-gender females (CF) selected based on the availability to ALT and AST blood levels.

The time under observation was divided into 2 intervals: from first blood test to immediately before GAHT initiation and from the start of GAHT to the most recent blood test. The date of the first filled GAHT prescription was assigned a value of 0; thus, pre-GAHT time had negative values and time post-GAHT initiation time had positive values (in years). For cisgender referents, time 0 was assigned based on the GAHT initiation of their matched transgender counterparts, even if their matched transgender participant contributed no data on ALT or AST levels.

Statistical Analysis

All data analyses were conducted using SAS, version 9.4 (SAS Institute). Patient’s level characteristics were reported using means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

For the longitudinal analysis, we used linear mixed models to characterize the change in AST and ALT over time level in relation to HT use among TM and TF participants in comparison to reference CF and CM groups. Obesity and alcohol intake are the 2 most common factors that may influence ALT/AST levels.[47–52] For this reason, all models included body mass index (BMI), and alcohol use or abuse (yes or no) at baseline. The alcohol use/abuse variable was ascertained from the diagnostic codes (Appendix Table 1). As it was not possible to maintain matching strata due to inconsistently available data for ALT and AST, all models also adjusted for race/ethnicity, age and study site.

The linear mixed models accounted for within-subject variation in repeated measures and allowed modeling of heterogeneity in the changes of AST and ALT over time across individuals by adding a random time slope. To examine the change of AST and ALT before and after HT separately, we centered the time variable on HT initiation date and coded it as linear splines with a knot at HT initiation. Below are the scalar forms of the main linear mixed model for AST:

$$\begin{aligned}\mathrm{AST}_{ij} &= \beta_0 + \mathrm{b}_{0i} + \beta_1 \mathrm{trans}_{ij} + \beta_2 \mathrm{time\_ht}_{ij} + \mathrm{b}_{1i} \mathrm{time\_ht}_{ij} \\ &+ \beta_3 \mathrm{posttime}_{ij} + \mathrm{b}_{2i} \mathrm{posttime}_{ij} \quad \beta_4 \mathrm{trans}_{ij} * \mathrm{time\_ht}_{ij} \\ &+ \beta_5 \mathrm{trans}_{ij} * \mathrm{posttime}_{ij} \\ &+ \beta_6 * \mathrm{Age} + \beta_7 * \mathrm{alcohol} + \beta_8 * \mathrm{race} + \beta_9 * \mathrm{BMI} + e_{ij} \\ \mathrm{ALT}_{ij} &= \beta_0 + \mathrm{b}_{0i} + \beta_1 \mathrm{trans}_{ij} + \beta_2 \mathrm{time\_ht}_{ij} + \mathrm{b}_{1i} \mathrm{time\_ht}_{ij} \\ &+ \beta_3 \mathrm{posttime}_{ij} + \mathrm{b}_{2i} \mathrm{posttime}_{ij} \quad \beta_4 \mathrm{trans}_{ij} * \mathrm{time\_ht}_{ij} \\ &+ \beta_5 \mathrm{trans}_{ij} * \mathrm{posttime}_{ij} \\ &+ \beta_6 * \mathrm{Age} + \beta_7 * \mathrm{alcohol} + \beta_8 * \mathrm{race} + \beta_9 * \mathrm{BMI} + e_{ij};\end{aligned}$$

where, *trans* indicates the transgender status (vs cisgender), *time_ht* is the centered time variable (negative prior to HT and positive afterwards), *posttime* is the time interval from HT to the measurement of AST/ALT. $trans_{ij} * time\_ht_{ij}$ and $trans_{ij} * posttime_{ij}$ are interaction terms reflecting the difference in AST and ALT value changes between transgender and cisgender. subjects; b_{0i} is the random intercept for subject i; b_{1i} is the random slope over time before HT for subject i; and the sum $b_{1i} + b_{2i}$ is the random slope after HT for subject i.

As distributions of both liver enzyme concentrations were highly skewed, the ALT and AST values in all models were log-transformed. The linear regression coefficients from all models were exponentiated to obtain a ratio of mean liver enzyme values across categories of independent variables, and the final result was expressed as a relative difference (in %). For example, a regression coefficient of −0.14 would exponentiate to a ratio of 0.87, which represents a relative difference of −13%. Each model was also used to derive the pre- and post-GAHT changes over time (expressed as percent difference per 10 days) and 2 relative difference ratios (ratios-of-ratios). The first ratio-of-ratios compared pre- and post-GAHT changes within each group, and the second ratio-of-ratios compared post-GAHT change in each transgender group to that of their respective cis-gender referents. All measures of association were reported along with the corresponding 95% confidence intervals (CIs)

RESULTS

Characteristics of Study Participants

Table 1 summarizes participant characteristics and shows distributions of AST and ALT levels before and after HT initiation. The analytic data set included 624 TF and 438 TM participants compared to 4,090 CM and 4,797 CF referents. More than half of both transgender and cisgender participants were Non-Hispanic whites. Only 11% of the TF participants and just 2% of the TM cohort members were older than 55-years of age, whereas the corresponding proportions of CM and CF referents were 18% and 15%, respectively. TF study participants included greater proportion of individuals with BMI <25 kg/m^2 (44%) compared to TM participants (37%) and both reference groups (22% among CM and 34% among CF). The proportion of individuals with history of alcohol use/abuse across the 4 groups ranged from 11% among TF to 14.5% among CM. Following HT initiation, the average ALT level decreased from 32.5 to 27.3 IU/L among TF study participants but increased from 27.0 to 35.1 IU/L in the TM group. The corresponding changes for AST were less pronounced among TF persons (from 32.1 to 30.2 IU/L), but were still evident (31.7 to 37.2 IU/L) among TM persons (Table 1).

Changes in ALT and AST in TM Study Participants Compared to CM and CF Referents

The multivariable models evaluating longitudinal changes in ALT and AST values among TM study participants are summarized in Tables 2 and 3. As shown in Table 2, the overall liver enzyme levels among TM participants were lower than those in CM referents, and the relative difference was statistically significant for both ALT (−13%; 95% CI: −20%, −6.4%) and AST (β = −27%, 95% CI: −31, −23%). In the corresponding analyses comparing TM participants to CF referents (Table 3), the relative difference was in the opposite direction, but statistically significant only for ALT (7%, 95% CI: 2, 13%).

There was evidence of post-GAHT increase in both ALT and AST among TM subjects when compared to pre-GAHT changes and especially when compared to the corresponding change among referents. For AST, the ratios-of-ratios were 1.61 (95% CI: 1.13, 2.31) and 1.57 (95% CI: 1.06, 2.31) relative to CM and CF referents respectively. For ALT, the corresponding comparisons yielded the ratios-of-ratios (95% CIs) of 2.06 (1.67, 2.54) compared to CM participants (Table 2) and 1.90 (1.50, 2.40) compared to CF cohort members (Table 3).

Alcohol use/abuse was consistently associated with higher levels of both ALT and AST in all models. Hispanic ethnicity and BMI ≥ 25 kg/m^2 were also consistently associated with higher ALT compared to their respective reference categories; however, the corresponding results for Hispanic ethnicity and AST were only statistically significant in the model comparing TM and CF referents whereas BMI ≥ 25 kg/m^2 was only significantly associated with AST in the model comparing TM with CM. Compared to Non-Hispanic whites Non-Hispanic blacks had lower levels of ALT in both models, while AST concentrations did not differ significantly between the 2 groups.

Changes ALT and AST in TF Study Participants Compared to CM and CF Referents

As shown in Table 4, levels of liver enzymes were lower in the TF group overall compared to CM cohort members with relative differences of −13% (95% CI: −19, −7%) for AST and −19% (95% CI: −23, −16%) for ALT. By contrast, the same analyses for TF vs CF (Table 5) were in the opposite direction for ALT (relative difference: 12%; 95% CI: 7, 16%) and showed no appreciable difference for AST (relative difference: 1%; 95% CI; −5, 8).

Unlike the analyses for TM, TF participants did not experience appreciable changes in ALT or AST following GAHT initiation. The ratios-of-ratios in all analyses were close to 1.0 and all 95% CIs included the null value (Tables 4 and 5).

Compared to non-Hispanic whites, Non-Hispanic Blacks had lower ALT both in the model comparing TF to CM (relative difference: −6%, 95% CI: −10, −2%) and in the model comparing TF to CF (relative difference: −11%, 95% CI: −16, −8%) whereas Hispanics had significantly higher levels of liver enzymes in all analyses except one (AST for TF vs CM). Alcohol use/abuse was associated with higher concentrations of liver enzymes across all models. BMI ≥ 25 kg/m^2 was significantly associated with higher ALT and ALT in the models comparing TF with CM; however, the same association in the model comparing TF and CF was only significant for ALT (relative difference: 22%; 95% CI: 20, 26%), but not for AST (relative difference: 3%, 95% CI: −1, 6%).

DISCUSSION

In these longitudinal analyses, which incorporated follow up of over 10 years, we observed that TM persons experienced an increase in both ALT and AST levels following GAHT initiation compared to cisgender referents. By contrast, the same results for TF did not demonstrate clear GAHT-induced changes over time.

Levels of aminotransferases vary with age, sex, race and body mass index.[19,20] Among cisgender people, AST and ALT levels are typically higher in men than in women.[19,20,49] These observations along with GAHT-induced longitudinal changes observed among TM study participants appear to suggest the opposite effects of testosterone and estrogen on liver function; however, clinical significance of these effects requires further study.

Consistent with previous evidence,[47–51] our study data also demonstrated that persons who met the definition of overweight or obesity (BMI ≥ 25 kg/m^2), and those with evidence of alcohol use or abuse had significantly higher levels of ALT, whereas the results for AST were less pronounced and less consistent across models.

Relative to non-Hispanic whites, ALT was consistently higher in Hispanic study participants and significantly lower among non-Hispanic blacks. The corresponding racial/ethnic disparities were not as evident for AST. The potential factors that may explain the racial/ethnic differences in liver enzyme levels include lifestyle and diet, disparities in insulin resistance and metabolic syndrome, and variable distribution of adipose tissue.[52]

Previous publications reporting on temporal changes in ALT and AST levels following masculinizing GAHT initiation are summarized in Table 6. In one of the earliest

publications, Jacobeit and colleagues followed 17 TM patients who received care at a clinical center in Hamburg, Germany, and were treated with IM injections of 1000 mg of testosterone undecanoate administered every 12 weeks.[39] The levels of transaminases at baseline were 22 and 24 IU/L for ALT and AST, respectively, and were measured at 6-month intervals for up to 3 years. The results demonstrated no discernable changes in either parameter over the follow up period. These results differ somewhat from those reported in another study, which was also conducted in Germany but at a different clinical center, and followed 45 patients receiving testosterone undecanoate for up to 2 years.[37] The baseline concentrations in the second German study were somewhat lower (19 IU/L for ALT and 21 IU/L) than those reported in the Jacobeit et al publication, and follow up data demonstrated significant increases at 12 months of follow for both enzymes, and at 24 months for ALT. Similar increases at 12-month following initiation of the testosterone undecanoate protocol were found in a recent study that followed 53 TM patients from Ghent, Belgium and Oslo, Norway enrolled in the European Network for the Investigation of Gender Incongruence (ENIGI) cohort.[41] Both ALT and AST concentrations among ENIGI cohort members increased from baseline levels of 16 and 20 IU/L respectively, by an average of 4 IU/L, and both changes were statistically significant.

4 US-based studies and 1 study from Belgium evaluated the effects of shorter acting testosterone esters given as weekly or biweekly injections at doses ranging from 25 to 300 mg. All but one of these studies relied on retrospective chart review. The only study with prospective follow up was based on a relatively small (n = 12) cohort of patients who received masculinizing GAHT at a clinical center in Boston, MA.[40] The average ALT levels in that study increased from 19 IU/L at baseline to 24 IU/L after 12 months of treatment with 50–125 mg of testosterone cypionate or testosterone enanthate injected every 2 weeks. The corresponding increase for AST was from 21 to 25 IU/L; however, none of the observed differences was statistically significant due to the small sample size. The statistically significant upward trends in ALT and AST concentrations following weekly or biweekly testosterone injections were also reported in a study from Ghent Belgium[42] and in a recent study from Dallas, TX.[34] By contrast, 2 other US based studies[31,32] found no evidence that testosterone was associated with higher levels of either enzyme.

The literature evaluating changes in ALT and AST concentrations in relation to feminizing GAHT initiation is relatively sparse (Table 7). Among 53 TF members of the ENIGI cohort, 40 patients were treated with 4 mg/d of oral estradiol valerate and the remaining received transdermal 17-β estradiol patches at 100 μg/24 h.[41] After 12 months of follow up, the changes in ALT and AST levels among TF study participants were opposite to those observed among TM cohort members. Among those treated with oral estradiol, ALT decreased from 25 to 19 IU/L and AST decreased from 24 to 18 IU/L. The corresponding changes among estradiol patch users were from 30 to 21 IU/L for ALT and from 27 to 20 IU/L for ALT.

The results reported in the ENIGI study were not consistently confirmed elsewhere. For example, Jarin and colleagues performed a review of records on 44 TF adolescents and young adults receiving gender-affirming care at medical centers in Washington DC, Baltimore, MD and Cincinnati, OH.[31] Participants were treated with various GAHT

regimens; which included oral estradiol 1–8 mg/d, intramuscular injections 20–80 mg monthly, or 0.025–0.2 administered subcutaneously once a week, but the data were analyzed together. The laboratory analysis results at baseline were compared to those obtained at 1–3, 4–6, and more than 6 months after feminizing GAHT initiation. The levels of liver enzymes decreased modestly from 25 to 17 IU/L for ALT and from 20 to 18 IU/L for AST; only the former change was statistically significant. In another study based on the chart review performed at an academic clinical center in Kentucky, the direction of ALT change was similar (from 27 IU/L at baseline to 24 IU/L at 6–18 months of follow up), but not statistically significant whereas no discernable change was observed for AST.[32] More recently, SeRelle and colleagues conducted a chart review to extract clinical data on TF patients treated at a large county hospital and community clinic in Dallas, TX.[34] Unlike other studies, SoRelle et al did not follow the same participants over time. Instead, levels of transaminases in that study were compared in 87 GAHT naïve TF patients and 133 TF patients who had been receiving GAHT for at least 6 months. In contrast to other reports, the average concentration of ALT was significantly higher in the GAHT-treated group relative to the GAHT-naïve group (28 vs 21 IU/L), whereas the corresponding difference for AST (21 vs 19 IU/L) was small and not statistically significant.

Several methodological features distinguish our study from the above-referenced earlier reports. First, the STRONG cohort provided de-identified clinical data that allowed evaluation of ALT and AST levels in an unselected group of KP enrollees without requiring subject opt-in. The access to the EHR for the source population of all KP members permitted selecting male and female cisgender referents from the same geographic areas and with the same type of insurance. Another methodological advantage of our study is the relatively large cohort size and extended follow up, which enabled assessment of trajectories of the changes in ALT and AST concentrations before and after GAHT initiation. Finally, to our knowledge, ours is the only study that incorporated multivariable analyses of repeated ALT and AST measures controlling for demographic characteristics, BMI, and alcohol use.

The EHR-based data collection methods in the current study are also associated with limitations. In contrast to clinic-based studies, such as the ENIGI cohort, the laboratory parameters of interest in STRONG were not measured at *a priori* pre-specified intervals, and the total number of samples and the rates of sample collection differed across participants. It is possible that some of the study participants required ALT/AST monitoring due to underlying liver disease. It appears unlikely that this affected the study results given the total population size and the relatively small changes in enzyme levels. Further, although GAHT use within the KP system is well-documented and accurate[46], the lack of information on treatment received elsewhere leaves room of exposure misclassification. In theory, it is possible to ascertain GAHT-naïive participants at baseline based on hormone levels; however, these data were not available for the current analyses. Another limitation of the current data is the limited ability to examine the effects of specific hormone formulations, routes of administration, and doses. This is explained by the variability of GAHT protocols across study sites and years of cohort ascertainment. Creating the relatively homogeneous GAHT groups would require excessive fragmentation of the data especially considering that many of the study participants had changes in therapy over the follow up period. Finally, although we controlled for BMI, and alcohol use or abuse the information for these

covariates was available at baseline only. Future studies should consider including these factors as time-dependent variables.

The above limitations notwithstanding, the associations of alcohol use and elevated BMI with higher levels of transaminases, especially ALT, observed in our study are in keeping with expectations and offer reassurance about the validity of the underlying data. With respect to the association of GAHT with liver enzyme concentrations, our study results are in agreement with previous reports, which on balance indicate that TM persons may experience modest increases in ALT and AST levels following testosterone initiation. We observed no statistically significant association between feminizing GAHT and changes in the levels of ALT and AST. These findings together with limited and conflicting results reported elsewhere indicate that estradiol administered for the purpose of gender affirmation is unlikely to induce appreciable changes in liver enzyme levels. Although the observed association of masculinizing GAHT with ALT and AST levels requires further investigation, the overall influence of long-term GAHT appears modest, and not likely to reflect clinically meaningful changes in liver function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of the transgender and matched reference cohorts*

Participant characteristics	TF cohort (n = 624)	TM cohort (n = 438)	CM referents (n = 4090)	CF referents (n = 4797)
Membership site				
KPNC	359 (57.5)	300 (68.5)	2494 (61.0)	3026 (63.1)
KPSC	252 (40.4)	135 (30.8)	1536 (37.6)	1725 (36.0)
KPGA	13 (2.1)	3 (0.7)	60 (1.5)	46 (1.0)
Race/ethnicity				
Non-Hispanic white	348 (55.8)	271 (61.9)	2533 (61.9)	2914 (60.7)
Non-Hispanic black	47 (7.5)	45 (10.3)	338 (8.3)	469 (9.8)
Hispanic	119 (19.1)	69 (15.8)	653 (16.0)	812 (16.9)
Asian/Pacific Islander	70 (11.2)	31 (7.1)	412 (10.1)	425 (8.9)
Other/Unknown	40 (6.4)	22 (5.0)	154 (3.8)	177 (3.7)
Age at index date, y				
18–25	195 (31.3)	185 (42.2)	682 (16.7)	987 (20.6)
26–35	155 (24.8)	148 (33.8)	915 (22.4)	1235 (25.7)
36–45	122 (19.6)	58 (13.2)	903 (22.1)	988 (20.6)
46–55	81 (13.0)	37 (8.4)	870 (21.3)	859 (17.9)
>55	71 (11.4)	10 (2.3)	720 (17.6)	728 (15.2)
BMI at index date				
Normal weight/Underweight	275 (44.1)	161 (36.8)	918 (22.4)	1626 (33.9)
Obese	165 (26.4)	118 (26.9)	1431 (35.0)	1228 (25.6)
Overweight	144 (23.1)	142 (32.4)	1414 (34.6)	1603 (33.4)
Unknown	40 (6.4)	17 (3.9)	327 (8.0)	340 (7.1)
Alcohol use/abuse				
Yes	70 (11.2)	56 (12.8)	595(14.5)	566 (11.8)
No	554 (88.8)	382 (87.2)	3495(85.5)	4231 (88.2)
Lab test data available				

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Participant characteristics	TF cohort (n = 624)	TM cohort (n = 438)	CM referents (n = 4090)	CF referents (n = 4797)
ALT	618 (99.0)	432 (98.6)	4002 (97.8)	4619 (96.3)
AST	240 (38.5)	150 (34.2)	1469 (35.9)	1952 (40.7)
ALT levels				
pre-GAHT	24.0 (19.0)	20.0 (15.0)	28.0 (22.0)	19.0 (15.0)
on-GAHT	19.0 (14.0)	22.0 (18.0)	27.0 (20.0)	19.0 (15.0)
AST levels				
pre-GAHT	23.0 (12.0)	22.0 (12.0)	26.0 (18.0)	21.0 (12.0)
on-GAHT	21.0 (12.0)	23.0 (11.5)	25.0 (17.0)	22.0 (13.0)

*Calculated as n (%) for membership site, race/ethnicity, age, lab test, BMI, alcohol use/abuse, and as median (interquartile range) for ALT and AST average level. Percentages may not sum to 100 due to rounding.ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CF = cisgender females; CM = cisgender males; KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; TF = transfeminine; TM = transmasculine; GAHT = gender-affirming hormone treatment.

Table 2.

Multivariable models evaluating factors associated with levels of AST and ALT among TM and CM study participants

	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Gender identity (TM vs CM)	−13	−20, −5	−27	−31, −23
Site (KPNC vs other)	1	−4, 6	8	5, 12
Age group (y) vs 18–25				
26–35	3	−3, 9	9	5, 15
36–45	11	3, 17	13	8, 19
46–55	1	−5, 8	1	−3, 6
56+	−1	−7, 6	−8	−12, −3
Race/ethnicity (vs NHW)				
Non-Hispanic Black	3	−5, 11	−7	−11, −2
Hispanic	3	−3, 9	9	6, 14
Asian/Pacific Islander	−4	−10, 4	3	−1, 8
Other/Unknown	−9	−19, 2	4	−3, 12
Body mass index (kg/m^2) ≥25.0 vs <25.0	7	3, 13	30	26, 34
Alcohol use/abuse (yes vs no)	19	13, 25	11	6, 14
Time (10-d increments)				
Pre-GAHT	−2	−7, 2	−10	−12, −7
Post-GAHT	−7	−17, 5	1	−6, 8
Pre-GAHT × gender identity	21	1, 45	26	12, 42

	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Post-GAHT × gender identity	34	−15, 110	63	26, 114
Calculated adjusted average 10-d change (%)				
TM pre-GAHT	18	−1, 40	14	2, 28
TM post-GAHT	47	4, 108	89	54, 131
CM pre-GAHT	−2	−7, 3	−10	−13, −6
CM post-GAHT	−9	−17, 0	−8	−13, −4
Ratio-of-ratios for 10-d change among TM (post- vs pre-GAHT)	1.25	0.81, 1.92	1.65	1.28, 2.14
Ratio-of-ratios for post-GAHT 10-d change (TM vs CM)	1.61	1.13, 2.31	2.06	1.67, 2.54

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CM = cisgender males; GAHT = gender affirming hormone therapy; KPNC = Kaiser Permanente Northern California; TM = transmasculine, NHW = non-Hispanic White.

Table 3.

Multivariable models evaluating factors associated with levels of AST and ALT among TM and CF study participants

	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Gender identity (TM vs CF)	6	−2, 15	7	2, 13
Site (KPNC vs other)	4	0, 8	8	6, 12
Age group (y) vs 18–25				
26–35	1	−4, 5	1	−3, 5
36–45	3	−2, 8	3	0, 7
46–55	8	3, 15	12	7, 17
56+	21	15, 28	17	13, 22
Race/ethnicity (vs NHW)				
Non-Hispanic Black	−2	−7, 4	−12	−16, −8
Hispanic	8	3, 13	7	3, 11
Asian/Pacific Islander	1	−5, 8	−1	−5, 4
Other/Unknown	−3	−11, 6	1	−5, 8
Body mass index (kg/m^2) ≥25.0 vs <25.0	3	−1, 6	21	19, 25
Alcohol use/abuse (yes vs no)	11	6, 15	12	7, 15
Time (10-d increments)				
Pre-GAHT	2	−2, 5	−2	−5, 1
Post-GAHT	−5	−15, 6	1	−6, 8
Pre-GAHT × gender identity	13	−4, 31	17	4, 31

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	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Post-GAHT × gender identity	39	−12, 120	62	21, 116
Calculated adjusted average 10-d change (%)				
TM pre-GAHT	15	−1, 33	15	2, 28
TM post-GAHT	52	4, 122	88	49, 136
CF pre-GAHT	2	−2, 6	−2	−5, 1
CF post-GAHT	−3	−11, 6	−1	−6, 4
Ratio-of-ratios for 10-d change among TM (post- vs pre-GAHT)	1.32	0.85, 2.06	1.64	1.24, 2.17
Ratio-of-ratios for post-GAHT 10-d change (TM vs CF)	1.57	1.06, 2.31	1.90	1.50, 2.40

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CF = cisgender females; CI = confidence interval; GAHT = gender affirming hormone therapy; KPNC = Kaiser Permanente Northern California; TM = transmasculine, NHW = non-Hispanic White.

Table 4.

Multivariable models evaluating factors associated with levels of AST and ALT among TF and CM study participants

	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Gender identity (TF vs CM)	−13	−19, −7	−19	−23, −16
Site (KPNC vs other)	2	−3, 6	8	5, 11
Age group (y) vs 18–25				
26–35	2	−4, 8	8	4, 13
36–45	12	5, 19	12	7, 17
46–55	2	−4, 8	0	−4, 4
56+	1	−5, 7	−8	−12, −4
Race/ethnicity (vs NHW)				
Non-Hispanic Black	7	0, 15	−6	−10, −2
Hispanic	4	−2, 9	9	5, 14
Asian/Pacific Islander	−4	−10, 3	3	−1, 8
Other/Unknown	−7	−16, 5	3	−3, 11
Body mass index (kg/m^2) ≥25.0 vs <25.0	7	3, 13	31	27, 35
Alcohol use/abuse (yes vs no)	21	15, 27	12	7, 16
Time (10-d increments)				
Pre-GAHT	−2	−7, 2	−10	−12, −6
Post-GAHT	−7	−16, 5	1	−6, 8
Pre-GAHT × gender identity	−10	−24, 6	−24	−32, −15

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	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Post-GAHT × gender identity	6	−21, 45	7	−12, 30
Calculated adjusted average 10-d change (%)				
TF pre-GAHT	−12	−25, 3	−31	−38, −23
TF post-GAHT	−13	−28, 7	−26	−34, −16
CM pre-GAHT	−2	−7, 2	−9	−12, −6
CM post-GAHT	−9	−16, 0	−9	−13, −4
Ratio-of-ratios for 10-d change among TF (post- vs pre-GAHT)	1.00	0.75, 1.32	1.08	0.90, 1.29
Ratio-of-ratios for post-GAHT 10-d change (TF vs CM)	0.96	0.77, 1.19	0.81	0.71, 0.93

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CM = cisgender males; GAHT = gender affirming hormone therapy; KPNC = Kaiser Permanente Northern California; TF = transfeminine, NHW = non-Hispanic White.

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Table 5.

Multivariable models evaluating factors associated with levels of AST and ALT among TF and CF study participants

	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Gender identity (TF vs CF)	1	−5, 8	14	9, 19
Site (KPNC vs other)	4	1, 8	8	5, 11
Age group (y) vs 18–25				
26–35	0	−5, 5	0	−4, 4
36–45	4	−1, 9	3	−1, 7
46–55	8	3, 15	11	6, 15
56+	21	14, 27	15	11, 20
Race/ethnicity (vs NHW)				
Non-Hispanic Black	1	−5, 6	−11	−16, −8
Hispanic	8	4, 14	6	3, 11
Asian/Pacific Islander	1	−5, 7	0	−4, 4
Other/Unknown	0	−9, 9	2	−5, 8
Body mass index (kg/m^2) ≥25.0 vs <25.0	3	−1, 6	22	20, 26
Alcohol use/abuse (yes vs no)	13	8, 17	13	8, 16
Time (10-d increments)				
Pre-GAHT	2	−2, 5	−2	−5, 1
Post-GAHT	−4	−14, 6	1	−6, 8
Pre-GAHT × gender identity	−13	−24, 0	−27	−34, −17

	AST		*ALT*	
Parameter of interest	**Difference (%)**	**95% CI**	**Difference (%)**	**95% CI**
Post-GAHT × gender identity	−2	−27, 34	0	−18, 23
Calculated adjusted average 10-d change (%)				
TF pre-GAHT	−11	−22, 1	−29	−35, −20
TF post-GAHT	−16	−33, 5	−27	−36, −16
CF pre-GAHT	2	−2, 5	−2	−5, 1
CF post-GAHT	−2	−10, 6	−1	−6, 5
Ratio-of-ratios for 10-d change among TF (post- vs pre-GAHT)	0.94	0.71, 1.26	1.02	0.84, 1.23
Ratio-of-ratios for post-GAHT 10-d change (TF vs CF)	0.86	0.68, 1.09	0.74	0.64, 0.85

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CF = cisgender females; GAHT = gender affirming hormone therapy; KPNC = Kaiser Permanente Northern California; TF = transfeminine, NHW = non-Hispanic White.

Table 6.

Summary of the published studies evaluating changes in ALT and AST concentrations in relation to masculinizing GAHT

Reference	Data source	Age (y)	GAHT	ALT (IU/L)*	AST (IU/L)*	Analysis	Statistical test results
Jacobeit et al, 2009 [38]	Prospective evaluation of 17 patients followed at a clinical left in Hamburg, Germany	Mean: 34 Range: 23–47	TU: 1000 mg IM every 12 wk. first 2 injections were 6 wk apart	Baseline: 22 6 mo: 23 12 mo: 21 18 mo: 24 24 mo: 22 30 mo: 24 36 mo: 22	Baseline: 24 6 mo: 25 12 mo: 23 18 mo: 24 24 mo: 25 30 mo: 22 36 mo: 23	Wilcoxon test for each follow up vs baseline	All $P > .05$ for ALT All $P > .05$ for AST
Chandra et al, 2010[40]	Prospective evaluation of 12 patients followed at a clinical center in Boston, MA	Mean: 29 SD: 9	TC or TE: 50–125 mg IM every 2 wk.	Baseline: 19 12 mo: 24	Baseline: 21 12 mo: 25	Paired *t*-test	$P = .22$ for ALT $P = .22$ for AST
Mueller et al, 2010[37,†]	Prospective evaluation of 45 patients followed at a clinical center in Erlangen, Germany	Mean: 30.4 SD: 9	TU: 1000 mg IM every 12 wk.	Baseline: 20 12 mo: 24 24 mo: 23	Baseline: 19 12 mo: 22 24 mo: 21	Tukey-Kramer test for each follow up vs baseline	All $P = .01$ for ALT $P = .08$ for AST at 12 mo $P = .30$ for AST at 24 mo
Wierckx et al, 2014[41]	Prospective evaluation of 53 patients from 2 sites of the European Network for the Investigation of Gender Incongruence (ENIGI): Ghent, Belgium and Oslo, Norway	*Ghent* Mean: 27 SD: 9 *Oslo* Mean: 22 SD: 5	TU: 1000 mg IM first 2 injections were 6 wk apart then every 12 wk	Baseline: 16 12 mo: 20	Baseline: 20 12 mo: 24	Paired *t*-test or Wilcoxon test (not specified)	$P = .02$ for ALT $P = .01$ for AST
Tack et al., 2016[42]	Chart review of 38 patients followed at a clinical left in Ghent, Belgium	Mean: 17	T esters: 50–125 mg IM every 2 wk	Baseline: 17 6 mo: 19 12 mo: 20	Baseline: 19 6 mo: 21 12 mo: 21	Student *t*-test or Wilcoxon test (not specified) for each follow up vs baseline	$P = .08$ for ALT at 6 mo $P = .045$ for ALT at 12 mo $P = .03$ for AST at 6 mo $P = .003$ for AST at 12 mo
Jarin et al, 2017[31]	Chart review on 72 patients followed at 4 clinical lefts in DC (2), MD and OH	Mean: 16 Range: 13–22	T NOS: 25–100 mg SQ weekly	Baseline: 21.1 1–3 mo: 21.7 4–6 mo: 26.9 >6 mo: 20.0	Baseline: 18.8 1–3 mo: 20.1 4–6 mo: 25.9 >6 mo: 19.5	Repeated measures ANOVA	$P > .05$ for ALT $P > .05$ for AST
Fernandez et al, 2017[32]	Chart review on 19 patients followed at a clinical center in Lexington, KY	Mean: 27 Range: 19–47	T NOS: IM, mean dose 11 mg/d.	Baseline: 23 3–6 mo: 19 6–18 mo: 16	Baseline: 23 3–6 mo: 23 6–18 mo: 22	Paried *t*-test for each follow up vs baseline	All $P > .05$ for ALT All $P > .05$ for AST
SoRelle et al. 2019[34]	Chart review on 62 GAHT naïve and 89 patients on GAHT from a county hospital and community clinic in Dallas, TX	Mean: 30	TC: 25–300 mg IM every 1–2 wk [98% subjects]	Baseline: 17 >6 mo: 23	Baseline: 18 >6 mo: 23	Mann-Whitney test	$P < .001$ for ALT $P < .005$ for AST

*Reported as a mean or median value, converted from SI units, if necessary.

†Data overlap with earlier study Mueller et al, 2007.ALT = alanine aminotransferase; AST = aspartate amniotransferase; GAHT = gender affirming hormone therapy; IM = intramuscular; IU/L = international units/liter; NOS = not otherwise specified; SQ = subcutaneous; T = testosterone; TU = testosterone undecanoate; TC = testosterone cypionate, TE = testosterone enanthate.

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Table 7.

Summary of the published studies evaluating changes in ALT and AST concentrations in relation to feminizing GAHT

Reference	Data source	Age (y)	GAHT	ALT (IU/L)*	AST (IU/L)*	Analysis	Statistical test results
Wierckx et al, 2014[41]	Prospective evaluation of 53 patients from 2 sites of the European Network for the Investigation of Gender Incongruence (ENIGI): Ghent, Belgium and Oslo, Norway	*Ghent* Mean: 32 SD: 15 *Oslo* Mean: 19 SD: 2	*Oral estrogen* EV 4 mg PO daily *Estrogen patch* 17-β estradiol: 100 μg/24 h	*Oral estrogen* Baseline: 25 12 mo: 19 *Estrogen patch* Baseline: 30 12 mo: 21	*Oral estrogen* Baseline: 24 12 mo: 18 *Estrogen patch* Baseline: 27 12 mo: 20	Paired *t*-test or Wilcoxon test (not specified)	*Oral estrogen* $P = .01$ for ALT $P < .001$ for AST *Estrogen patch* $P = .12$ for ALT $P = .013$ for AST
Jarin et al, 2017[31]	Chart review on 44 patients followed at 4 clinical centers in Washington, DC (2), Baltimore, MD and Cincinnati, OH	Mean: 18 Range: 14–25	Estradiol NOS: 1 −8 mg PO daily; 20 −80 mg IM monthly; or 0.025 −0.2 SQ weekly	Baseline: 25.4 1−3 mo: 23.5 4–6 mo: 15.2 >6 mo: 17.3	Baseline: 20.1 1–3 mo: 24.9 4–6 mo: 19.6 >6 mo: 17.5	Repeated measures ANOVA	$P < .05$ for ALT; at 4–6 mo and after 6 mo $P > .05$ for AST
Fernandez et al, 2017[32]	Chart review on 33 patients followed at a clinical center in Lexington, KY	Mean: 31 Range: 16–56	Estradiol NOS: PO 1.4–1.7 mg/d. or SQ or IM (dose NOS)	Baseline: 27 3–6 mo: 28 6–18 mo: 24	Baseline: 23 3–6 mo: 22 6–18 mo: 23	Piared *t*-test for each follow up vs baseline	All $P > .05$ for ALT All $P > .05$ for AST
SoRelle et al, 2019[34]	Chart review on 87 GAHT naïve and 133 patients on GAHT from a county hospital and community clinic in Dallas, TX	Mean: 33	Estradiol NOS: 2–8 mg PO daily; or EV 5–40 mg (93% subjects)	Baseline: 21 >6 mo: 28	Baseline: 21 >6 mo: 19	Mann-Whitney test	$P < .005$ for ALT $P > .05$ for AST

*Reported as a mean or median value, converted from SI units, if necessary.ALT = alanine aminotransferase; AST = aspartate aminotransferase; EV = estradiol valerate; GAHT = gender affirming hormone therapy; IM = intramuscular; IU/L = international units/liter; NOS = not otherwise specified; PO = per os (orally); SQ = subcutaneous.