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## Liver function in transgender persons: Challenges in the COVID-19 era

Charalampos Milionis, Ioannis Ilias, Eftychia Koukkou

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### Abstract

Transgender persons constitute a non-negligible percentage of the general population. Physical gender-transitioning in trans persons is mainly achieved with hormonal cross-sex therapy and sex reassignment surgeries that aim to align bodily appearance with gender identity. Hormonal treatment acts *via* suppressing the secretion of the endogenous sex hormones and replacing them with the hormones of the desired sex. The administration of testosterone is the typical masculinizing treatment in trans men, whilst trans women are routinely treated with estradiol agents in combination with anti-androgens or gonadotrophin-releasing hormone agonists if testes are present. Exogenous androgenic steroids, estradiol agents, and anti-androgens have been implicated in a series of hepatotoxic effects. Thus, liver integrity is a major concern with the long-term administration of cross-sex therapy. Hepatic tissue is susceptible to coronavirus disease 19 (COVID-19) through various pathophysiological mechanisms. Special consideration should be paid to minimize the risk of hepatic damage from the potential cumulative effect of COVID-19 and gender-affirming treatment in transgender patients. Appropriate care is significant, with continuous laboratory monitoring, clinical observation and, if needed, specific treatment, especially in severe cases of infection and in persons with additional liver pathologies. The pandemic can be an opportunity to provide equal access to care for all and increase the resilience of the transgender population.

**Key Words:** Transgender persons; Drug induced liver injury; COVID-19

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**Core Tip:** Transgender persons may account for approximately up to 0.3% of the population. Their access to health care and medications may be hampered in the coronavirus disease 19 (COVID-19) era. The effects of COVID-19 *per se* on the liver may not be negligible. In this concise review we ponder on these effects, honed on transgender persons.

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## INTRODUCTION

In humans, as in most mammals, biological sex is determined by sex chromosomes X and Y. The development to a male or female sex depends on the presence of a single sex-regulatory genetic locus, the sex-determining region Y (SRY) gene, on the male-limited Y chromosome. Expression of SRY early in the embryonic life leads the bipotential embryonic gonad to differentiate into testis through the activation of male-specific developmental pathways. In contrast, ovaries develop when SRY is absent. The first signs of sexual differentiation of gonads occur by the sixth gestational week in humans. Sex hormones induce further sexual differentiation in gonads and non-gonadal tissues and organs and in this way, they form the sex phenotype[1].

Gender identity is a person's self-perception of belonging to a particular gender type (masculine, feminine, a combination, or none of both) and does not always align with biological sex. Gender dysphoria is the sense of distress which derives from the discordance between an individual's gender identity and sex features[2]. The term 'transgender' refers to persons whose gender identity (and possibly gender expression) differs from what is normative for their biological sex (most usually assigned at birth). In particular, transgender males (trans men) are persons who self-identify as male, although they were labeled as female at birth and transgender females (trans women) are persons who have the gender identity of a female, despite having been assigned male sex at birth. Furthermore, the transgender term also includes persons whose gender identity does not conform to the classical dipole of male/female[3]. It is estimated that about 0.355% of the population identify themselves as transgender. However, the prevalence of trans people who receive medical care for gender-transitioning is only around 0.009%[4].

After the diagnosis of gender dysphoria is established and if physical transitioning is desired, a framework for ongoing care needs to be applied. An appropriate management may include psychotherapy, hormonal treatment, and surgical sex reassignment. These approaches are considered to be safe and effective both in short- and in the long-term[5]. Gender-affirming hormonal treatment improves uneasiness from perceived inconsistencies between one's biological sex and gender identity. It acts *via* suppressing the secretion of the endogenous sex hormones and replacing them with the hormones of the desired sex. As with any medical therapy, the awareness of potential side effects is important. Thus, regular clinical evaluation for physical changes and laboratory monitoring of potential adverse effects in response to cross-sex hormonal therapy is necessary. Typical follow-up is performed every three months during the first year of treatment and then once or twice yearly[6]. Tables 1 and 2 depict a model timeline for monitoring clinical course and laboratory parameters when treating trans men and women, respectively.

## HEALTH CARE FOR TRANSGENDER PEOPLE

Transgender people have a series of special medical needs which create an inevitable regular engagement with health care services. In terms of psychiatric care, a firm diagnosis of gender dysphoria and subsequently psychotherapy on finding ways to integrate each person's diverse gender identity into the personal background and social circumstances are fundamental. Trans people often encounter stigmatization and discrimination which can have a profound adverse effect on their emotional well-being. Therefore, they need to access responsive and competent mental health services to cope with depression, suicidality, anxiety, and substance use which are disproportionately frequent among transgender populations[7,8].

Gender-transitioning is performed with medical interventions, including hormonal therapy and sex reassignment surgeries that aim to align physical appearance with gender identity. Typical trans-feminine (male-to-female) hormonal treatment includes estrogens and testosterone-lowering agents, such as anti-androgens or gonadotrophin-releasing hormone (GnRH) agonists, whilst the administration of testosterone is the mainstream approach in transmasculine (female-to-male) hormonal

**Table 1** Timeline for monitoring trans men

<b>Laboratory evaluation</b>	
Baseline blood tests	Testosterone, estradiol; CBC (including Hct or Hgb); Liver enzymes, lipid profile, creatinine; Fasting glucose (and HbA1c or oral glucose tolerance test if diabetes is suspected)
4-6 wk after starting treatment	Testosterone, estradiol; CBC (including Hct or Hgb)
3, 6, 9, and 12 mo after starting treatment	Testosterone, estradiol; CBC (including Hct or Hgb); Liver enzymes, lipid profile, creatinine (every 6 mo); Fasting glucose (every 6 mo)
Semiannually or annually thereafter	Testosterone, estradiol; CBC (including Hct or Hgb); Liver enzymes, lipid profile, creatinine; Fasting glucose (every 6 mo)
In 50 yr of age (only if treatment is stopped or when risk factors for osteoporosis exist) and accordingly thereafter	Bone mineral density measurement
Individualized approach	Screening tests for breast and endometrial cancer (with no prior hysterectomy)
<b>Clinical assessment</b>	
Regular clinical examination (including body weight and blood pressure measurements), evaluation of masculinization, recording and monitoring of potential side effects	

CBC: Complete blood count; Hct: Hematocrit; Hgb: Hemoglobin; HbA1c: Glycated hemoglobin.

**Table 2** Timeline for monitoring trans women

<b>Laboratory evaluation</b>	
Baseline blood tests	Testosterone, estradiol; Prolactin; CBC; Liver enzymes, lipid profile, creatinine; Fasting glucose (and HbA1c or oral glucose tolerance test if diabetes is suspected); Electrolytes; Coagulation tests (in case of high risk for thrombosis)
1 mo after starting treatment	CBC; Liver enzymes, lipid profile, creatinine; Electrolytes (if taking spironolactone)
3, 6, 9, and 12 mo after starting treatment	Testosterone, estradiol; CBC; Liver enzymes, lipid profile, creatinine (every 6 mo); Fasting glucose (every 6 mo); Electrolytes (if taking spironolactone)
Semiannually or annually thereafter	Testosterone, estradiol; Prolactin (every 2 yr); CBC; Liver enzymes, lipid profile, creatinine; Fasting glucose (every 6 mo); Electrolytes (if taking spironolactone)
In 60 yr of age (or earlier if treatment is stopped after orchiectomy or when risk factors for osteoporosis exist) and accordingly thereafter	Bone mineral density measurement
Individualized approach	Screening tests for prostate and breast cancer
<b>Clinical assessment</b>	
Regular clinical examination (including body weight and blood pressure measurements), evaluation of feminization, recording and monitoring of potential side effects	

CBC: Complete blood count; Hct: Hematocrit; Hgb: Hemoglobin; HbA1c: Glycated hemoglobin.

therapy. The goal is to achieve and maintain sex hormone levels in the normal physiologic range of the desired gender. For non-binary persons, regimens and dosages should be modified according to the clinical targets[9]. Surgical reconstruction techniques focus on transforming genitals and secondary sex characteristics[10]. Hence, the process of gender-transitioning is inextricably related to the utilization of specialized medical services.

Trans people have special sexual and reproductive medical needs. Comprehensive cancer screening based on the retained organs[11] and prevention and management of sexually transmitted diseases[12] are important aspects of transgender care. Further possible needs for health services are linked to gamete storage and assisted reproduction[13]. Nonetheless, caring for transgender individuals also includes general coverage for possible co-existing morbidities which are not directly related to gender-transitioning.

## IMPACT OF THE COVID-19 PANDEMIC ON TRANSGENDER HEALTH CARE

As a medically and socially vulnerable population, transgender people face numerous disparities in accessing health care. Most common difficulties are due to structural (related to systemic disadvantages) and interpersonal (reflecting negative personal attitudes) barriers within the health care context[14]. Firstly, there is a lack of health professionals who are specialized in providing gender-affirming care, whilst others may not be willing to treat transgender persons[15]. Secondly, trans individuals are often denied health insurance either for procedures that are routinely covered for their cisgender peers or for hormonal treatment and surgical sex reassignment. Low personal income further aggravates the lack of access to health services[16]. Thirdly, discriminative attitudes on the part of health personnel may lead transgender persons to postpone or even avoid seeking care[17].

The pandemic created unprecedented difficulties for trans persons both in attaining physical and social well-being and in accessing health care. The socio-economic circumstances of the coronavirus disease 19 (COVID-19) outbreak disproportionately affected transgender people in comparison with the general population. Increased unemployment rate and lower available income impeded access to both basic and expert clinical care[18]. Restricted access to mental health care and social support resulted in a loss of emotional resilience against the effects of gender-minority stress[19]. Although the latest variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are less pathogenic, the pandemic is still present and continues to fuel deficiencies in caring for trans people.

Gender-affirming care requires ongoing medical support for assessment, modification, and monitoring of the transition process. However, restrictive policies during the pandemic led most hospitals to cancel or postpone elective procedures (such as routine consultations and scheduled surgeries) in order to give priority to the management of COVID-19 cases. Thus, the accessibility to hormonal therapy and surgical sex reassignment became more difficult[20]. Shortages of medications also occurred[21]. These conditions arrested or hindered gender-transition for many trans persons and caused psychological distress due to the regression to undesired sex features[22]. Despite the withdrawal of most restrictive measures, much effort is still needed to normalize the situation.

## LIVER FUNCTION IN TRANSGENDER MALES

The administration of testosterone is the typical masculinizing treatment in trans men[23]. There are certain modifications of the testosterone molecule which maintain or even enhance its virilizing effects but change its pharmacodynamic properties (Figure 1). The C-17 $\alpha$  alkylation permits the oral administration of the substance by inhibiting its metabolic deactivation in the liver. The C-17 $\beta$  esterification (such as in testosterone enanthate, cypionate, and undecanoate) increases the potency and duration of action, but it requires a parenteral administration. However, the C-17 $\alpha$  alkylated androgenic steroids have been implicated in causing liver damage, including prolonged cholestasis, hepatic peliosis, nodular regenerative hyperplasia, hepatic adenomas, and hepatocellular carcinoma. In contrast, the C-17 $\beta$  esterified molecules rarely cause cholestasis, but their prolonged use may increase the risk of hepatic tumors and nodular transformation, seemingly at a lower rate in comparison with the C-17 $\alpha$  alkylated products[24]. Figure 2 presents the molecular structure of the most commonly used injectable preparations of testosterone in gender-affirming treatment.

C-17 $\alpha$  alkylated derivatives of testosterone are not recommended for hormonal treatment of transgender males and thus, serious hepatic toxicity from oral pharmaceutical forms is usually avoided. Nonetheless, hepatotoxicity due to the long-term administration of exogenous testosterone esters is always a concern during therapy of transgender males. For this reason, trans men under androgen therapy should be monitored every three months during the first year of treatment and then semi-annually or annually[25]. Aspartate and alanine aminotransferases (AST and ALT, respectively) are the most commonly used biomarkers of liver injury. These enzymes catalyze the conversion of  $\alpha$ -ketoglutarate and an amino acid to glutamate and another product[26]. The initiation of masculinizing gender-affirming treatment is expected to induce a slight increase in the blood levels of both AST and ALT. However, the clinical significance of these changes is usually minimal[27].

Testosterone acts through binding to the intracellular androgen receptors. This ligand binding results in conformational changes which in turn cause the translocation of the testosterone/receptor complex to the nucleus. There, it dimerizes and binds to androgen response elements on DNA, modulating thereby the transcription of specific genes that are important in cell development[28]. The mechanisms of the hepatotoxic effects of exogenous testosterone remain unclear. An impairment of cellular growth processes and an increase in oxidative stress within hepatocytes – both mediated by androgen receptors – are possible causes of liver damage related to the use of pharmaceutical forms of testosterone[29]. The etiology of cholestasis caused by testosterone derivatives is even more vague. It may be due to a disruption of the microfilaments within the hepatocytes that reduces their ability to transport bile[30].

Transmasculine gender-affirming therapy usually has no adverse effects on hepatic function[31]. Exogenous testosterone may cause minor serum enzyme elevations, but profound cholestasis, hepatic peliosis, and benign and malignant liver tumors are only theoretical risks. However, caution is

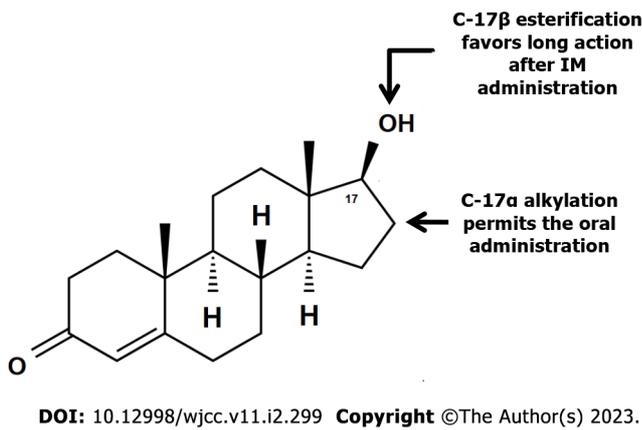


Figure 1 The testosterone molecule - substitution at C-17 favors oral administration or long duration of action.

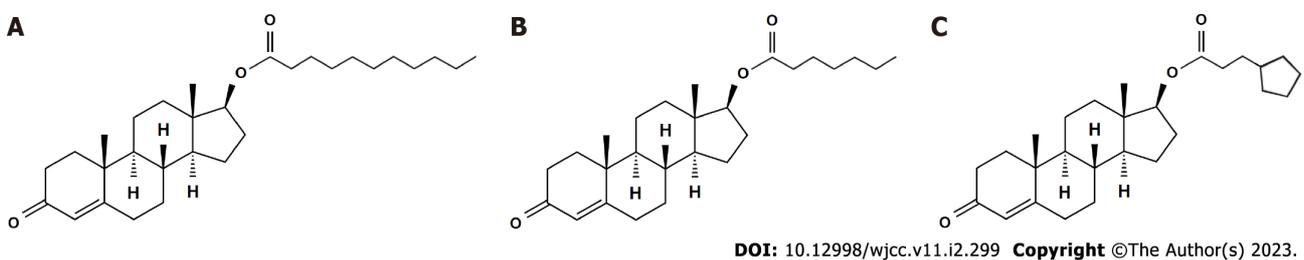


Figure 2 Injectable testosterone semi-synthetic analogues. A: Undecanoate; B: Enanthate; C: Cypionate.

necessary when administering masculinizing treatment to patients with pre-existing liver disease due to the risk of deterioration of hepatic function. The principal step in managing potential liver damage is the pause of the administration of the androgenic steroid. Although some trans men may be disappointed with this decision, it is important to proceed to this action. Merely decreasing the dose of testosterone or switching to another formulation is not appropriate. Hepatotoxicity is usually reversible with the cessation of therapy, but full recovery often needs an extended period of time.

## LIVER FUNCTION IN TRANSGENDER FEMALES

Transgender women are routinely treated with estradiol agents combined with anti-androgens or GnRH agonists if testes are present. The administration of estrogens has been rarely associated with liver disease at the dosages that are nowadays used either for contraception in cisgender females or for hormonal replacement treatment of postmenopausal women. Intrahepatic complications are more common with high doses of estrogens which is not a routine practice in gender-transition of trans females. Nevertheless, treatment with estrogens has been linked to susceptibility to venous thrombosis because of alterations in the hepatic synthesis of coagulation factors and antithrombin III. The risk is markedly greater with oral treatment because the intestinal absorption is rapid and yields high concentrations of hormone in the portal circulation[32]. Moreover, estrogens can cause a decrease in bile flow leading to intrahepatic cholestasis with pruritus and jaundice[33]. They may also be involved in the occurrence of nodular hyperplasia and hepatic benign and malignant tumors after long-term use, although the relevant evidence is not strong[34].

Exogenous estrogens, administered either orally or transdermally, induce physiologic processes that favor the formation of gallstones. Most clinical evidence derives from studies investigating the use of oral contraception or hormonal replacement therapy in cis women and the administration of estrogens for the treatment of prostate cancer in cis men. Accordingly, estrogen regimens are expected to increase the propensity of adverse biliary tract outcomes also in trans women receiving gender-affirming treatment. Indeed, therapy with exogenous estrogens can decrease nucleation time, enhance cholesterol saturation, and raise the biliary levels of arachidonate and prostaglandin E2. These effects are important risk factors which may result in cholelithiasis[35].

Cyproterone acetate is a steroidal anti-androgen that is routinely used in gender-transition of trans women. It inhibits the action of endogenous testosterone through blocking the androgen receptors. However, treatment with cyproterone acetate has been linked to liver-related adverse reactions. Most

cases appear to be modest and transient serum enzyme elevations. Nevertheless, instances of overt hepatotoxicity have been reported. The clinical features of hepatic injury may range from mildly symptomatic hepatitis with jaundice to acute liver failure. The relevant data have emerged mainly from studies of cis men receiving cyproterone acetate for advanced prostate cancer[36]. The relevant mechanism that leads to the liver damage is not clear. It is presumably an idiosyncratic reaction to the drug or its metabolites or an immunologically mediated response[37]. Occasional reports of hepatic cirrhosis and hepatocellular carcinoma induced by cyproterone acetate have also emerged[38]. In contrast, GnRH agonists (also used for suppression of gonadal testosterone) have not been implicated in causing clinically significant hepatotoxicity.

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## THE EFFECTS OF COVID-19 ON THE LIVER

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SARS-CoV-2 is the etiological agent that causes COVID-19. The respiratory tract is the main target site of SARS-CoV-2 infection, but dissemination and replication of the pathogen in several other tissues can also contribute to the clinical impact of COVID-19. Hepatic tissue is a frequent site of extrapulmonary involvement of SARS-CoV-2. The incidence of liver injury in patients with COVID-19 ranges between 15% and 53%, although these figures may be different with the new variants of the pathogen[39,40]. Most common clinical features of liver dysfunction in COVID-19 are non-specific and may include fever, fatigue, anorexia, nausea, vomiting, diarrhea, and abdominal pain. Jaundice may also occur in rare cases. The laboratory findings of liver injury in COVID-19 include various degrees of ALT and AST elevations often combined with hypoalbuminemia and hyperbilirubinemia. In patients with COVID-19, abnormal liver function tests are associated with a greater risk of transfer to the intensive care unit, mechanical ventilator support, and mortality. As with other chronic diseases, prognosis from infection with the novel coronavirus is worse in patients with pre-existing hepatic disease (viral hepatitis, fatty liver, cirrhosis, hepatoma)[41].

SARS-CoV-2 enters the host cells through the membrane bound angiotensin-converting enzyme 2 (ACE2) receptor. The spike glycoprotein of the virion is composed of S1 and S2 subunits and protrudes from the viral surface. Upon binding to ACE2, the S1 subunit is dissociated with the ACE2 receptor with the presence of transmembrane serine protease 2 (TMPRSS2). This process results in conformational changes that increase the stability of S2 subunit and permit the viral envelope-cellular membrane fusion [42]. The respiratory tract is not the unique tropism for SARS-CoV-2. In humans, ACE2 and TMPRSS2 are present in multiple extrapulmonary tissues. In particular, ACE2 is highly expressed in cholangiocytes and to a lesser degree in hepatocytes, whilst TMPRSS2 is also expressed in both the hepatocytes and cholangiocytes[43]. The hepatic presence of these proteins renders the liver an accessible organ to SARS-CoV-2.

Pathogenesis in liver injury from COVID-19 is probably due to various mechanisms[39,40]. Firstly, direct viral cytopathogenic insult of hepatocytes and cholangiocytes may cause hepatobiliary damage. Secondly, the hyperinflammatory response induced by the viral infection and the accompanying hypercytokinemia may cause tissue damage and organ failure, especially in the liver. Thirdly, hepatotoxicity could derive from the variety of antiviral drugs, corticosteroids, antibiotics, and antipyretics that are used for treatment of COVID-19 patients. Fourthly, hypercoagulable state associated with COVID-19 and the resultant thrombosis may cause hepatic degeneration[44]. Lastly, cardiac and respiratory failure may lead to circulatory compromise, causing thereby a hypoxic injury to the liver[45,46]. Nevertheless, several other underlying mechanisms may contribute to liver injury in COVID-19 patients. Moreover, the pathophysiological synergy of pre-existing liver disease and COVID-19 is possible and needs to be thoroughly evaluated.

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## MONITORING TRANSGENDER LIVER FUNCTION IN THE ERA OF THE PANDEMIC

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Currently, transgender people constitute a non-negligible percentage of the general population. Hormonal therapy is an essential component of gender-affirming treatment because it can lead to improvements in psychological functioning and quality of life among the recipients[47]. However, hepatotoxicity is a major concern with the long-term administration of either testosterone derivatives or oral estradiol and anti-androgens. The incidence of drug induced liver injury due to usual transmasculine and transfeminine hormonal regimens is seemingly low[48,49]. Nevertheless, monitoring of liver function on a regular basis is important[50] because of the severity of the potential hepatic impairment from gender-affirming pharmacotherapies and possible liver comorbidities among trans people. This strategy can assist in the prevention of therapeutic failures and in the avoidance of adverse side effects [51].

Protecting liver integrity of transgender people becomes even more crucial in case of a SARS-CoV-2 infection. In general, the interplay of immune mediators and drugs with hepatotoxic properties could synergistically increase the toxic effect on liver[52,53], although relevant evidence does not exist for trans patients with COVID-19. Furthermore, almost all the drugs prescribed for both the COVID-19

management and the cross-sex hormonal treatment are metabolized in the liver, hence an elevation of hepatic enzymes and possible drug induced liver damage due to a cumulative effect is expectable[54].

For the aforementioned reasons, special consideration should be paid to minimize the risk of hepatic damage from COVID-19 in these patients. For this purpose, assessment of trans persons with SARS-CoV-2 infection should include a thorough evaluation of hepatic function in addition to the investigation of primary respiratory manifestations. Furthermore, appropriate care with continuous laboratory monitoring, clinical observation and, if needed, specific treatment is significant, especially in cases of hospitalization. Liver function tests should be regularly observed, and viral hepatitis markers should be determined. Imaging studies of the liver, gallbladder, and biliary tract should be performed in case of abnormal laboratory findings. Cautious utilization of pharmacotherapies is also necessary. Gender-affirming hormonal treatment is not a contraindication of vaccination against COVID-19. Thus, transgender people should be advised to get vaccinated with initial and booster doses according to the general recommendations.

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## CONCLUSION

Although gender-transition *per se* does not imply a worse prognosis in COVID-19, prior vulnerabilities with regards to health problems and the impaired access to health care of trans people were exacerbated by the pandemic. Adverse hepatotoxic effects of cross-sex hormonal therapy, although uncommon in daily practice, become particularly important in case of SARS-CoV-2 infection. The possible synergistic impact of COVID-19 on liver both in the short- and in the long-term must not be neglected and requires proper investigation and management. A multicentric study may contribute to a deeper knowledge about this issue. The pandemic can be an opportunity to provide equal access to care for all and increase the resilience of the transgender population.

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## FOOTNOTES

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