Background of HCV-HIV Coinfection

Impact of HCV Coinfection

In the United States, approximately 5% of adults with chronic hepatitis C (HCV) infection have coinfection with HIV.[1] Among persons living with HIV in the United States, an estimated 15 to 30% have HCV coinfection, but these rates vary significantly based on the individual’s risk factor for acquiring HCV.[2,3,4,5] Coinfection with HIV accelerates the progression of hepatic fibrosis and results in a more aggressive course of liver disease (Figure 1).[6,7,8] Cirrhosis has been observed to occur 12 to 16 years earlier in persons coinfected with HCV and HIV compared with those who have HCV monoinfection.[9] For persons living with HIV who have HCV coinfection, liver-related morbidity and mortality is a prominent non-AIDS-related complication—up to 80 to 90% of liver-related deaths in persons living with HIV are attributable to HCV infection.[10,11] Unfortunately, individuals with HCV and HIV coinfection have decreased access to liver transplantation compared with persons with HCV monoinfection.[12] For all these reasons, treatment of HCV in persons with HIV coinfection should have a high priority. Historically, in the interferon era, treatment of HCV in persons with HIV-HCV coinfection had limited uptake, due to a low response rate with interferon-based therapy, a high rate of adverse effects, concerns for interactions with antiretroviral medications, and high prevalence of comorbidities.[13] The availability of highly effective all-oral direct-acting antiviral (DAA) regimens has completely changed the landscape of treating HCV in persons with HIV-HCV coinfection.

Historic Approach to Treatment

For individuals with HIV-HCV coinfection, initial trials with interferon monotherapy or dual therapy with interferon plus ribavirin were associated with very low sustained virologic response (SVR) rates and significant toxicity. Subsequently, studies showed higher SVR rates with peginterferon and ribavirin treatment (Figure 2), but these were still suboptimal, especially in persons with genotypes 1 or 4 (Figure 3).[14,15,16,17] The peginterferon and ribavirin combination regimen generated particularly low SVR rates among those with HCV genotype 1 (typically less than 30%). Further, the SVR rates with peginterferon and ribavirin were generally 15 to 25% lower in persons with HIV-HCV coinfection than with HCV monoinfection. In 2011, the addition of a first-generation HCV protease inhibitor (telaprevir or boceprevir) to peginterferon and ribavirin improved SVR rates with HCV genotype 1 to approximately 60% and slightly narrowed the gap in treatment response between persons with HIV-HCV coinfection and HCV monoinfection.[18,19,20,21] This triple therapy regimen, however, proved to be quite complex and challenging due to interactions with antiretroviral medications, greater pill burden, food requirements, and additional adverse effects. With the availability of newer all-oral DAA regimens that are highly effective, safe, convenient to take, the older regimens of peginterferon and ribavirin or peginterferon and ribavirin plus a first-generation protease inhibitor are no longer recommended for treatment of HCV.[22]
HCV Treatment Data in Persons with HIV Coinfection

Multiple studies using DAA-based therapy have demonstrated HCV treatment SVR rates in individuals with HIV-HCV coinfection that are comparable to those with HCV monoinfection (Figure 4), providing convincing evidence that persons with HIV-HCV coinfection should no longer be considered as a “treatment refractory” population. In these trials, most participants did not have cirrhosis and most had a CD4 count well above 200 cells/mm$^3$. More recently, however, a variety of observational cohort studies with heterogeneous cohorts of persons with HIV-HCV coinfection, including those with more advanced liver disease and lower CD4 cell counts, have shown comparable HCV SVR rates with HIV-HCV coinfection and HCV monoinfection. The following provides a summary of key clinical trials (in alphabetical order) involving DAA treatment of HCV infection in persons with HIV coinfection.

- **Daclatasvir plus Sofosbuvir** *(ALLY-2)*: In the phase 3, randomized, multi-center ALLY-2 trial, investigators enrolled 203 adults with HIV-HCV coinfection to receive HCV treatment with daclatasvir plus sofosbuvir. Hepatitis C treatment-naïve participants were randomized to receive either an 8-week or 12-week course of daclatasvir plus sofosbuvir, whereas all treatment-experienced participants received a 12-week course. Individuals with HCV genotype 1, 2, 3, or 4 were eligible. The HIV entry criteria required a CD4 count greater than 350 cells/mm$^3$ if not taking antiretroviral therapy, or at least 100 cells/mm$^3$ if on antiretroviral therapy and the HIV RNA level was less than 50 copies/mL. Participants receiving a 12-week regimen had excellent SVR 12 rates (96% in the treatment-naïve arm and 98% in the treatment-experienced arm), but only 76% of the treatment-naïve participants receiving 8 weeks of therapy achieved an SVR12.

- **Elbasvir-Grazoprevir** *(C-EDGE Coinfection)*: In this prospective single-arm, open-label clinical trial, investigators enrolled 218 adults with chronic HCV genotype 1, 4, or 6 and HIV coinfection to receive treatment with a 12-week course of elbasvir-grazoprevir once daily for 12 weeks. Among those enrolled, 86% had genotype 1a or 1b infection and 16% had compensated cirrhosis. The overall SVR12 rate was 96% by primary analysis, with the breakdown by genotype showing 96.5% for those with genotype 1a, 95.5% for genotype 1b, and 96.4% for genotype 4. All study participants with cirrhosis achieved an SVR12.

- **Glecaprevir-Pibrentasvir** *(EXPEDITION-2)*: This open-label, dual-arm, phase 3 trial enrolled adults with HCV (genotype 1, 2, 3, 4, 5, or 6) and HIV coinfection to receive HCV treatment with glecaprevir-pibrentasvir. The 137 participants without cirrhosis were assigned 8 weeks of HCV treatment and the 16 individuals with compensated cirrhosis received 12 weeks. The majority (63%) of participants had HCV genotype 1 and 18% were treatment-experienced (16% previously treated with an interferon-based regimen and 2% with a sofosbuvir-based regimen). All but 10 participants were taking raltegravir, dolutegravir, or rilpivirine as the antiretroviral therapy anchor drug. The overall SVR12 rate was 98%; one individual with HCV genotype 3 and cirrhosis experienced on-treatment HCV virologic breakthrough.

- **Ledipasvir-Sofosbuvir** *(ION-4)*: In this phase 3, open-label, multicenter study, investigators enrolled 335 adults with HCV genotype 1 or 4 who were coinfected with HIV to receive a 12-week course of ledipasvir-sofosbuvir. Enrollment included HCV treatment-naïve and HCV treatment-experienced individuals and those without cirrhosis and those with compensated cirrhosis. The HIV enrollment criteria required an HIV RNA level less than 50 copies/mL and a CD4 count greater than 100 cells/mm$^3$; antiretroviral regimens could include tenofovir DF-emtricitabine plus either efavirenz, rilpivirine, or raltegravir. Overall, 96% (321 of 335) of the study participants who received HCV treatment achieved an SVR12. The results were similar regardless of prior treatment status or presence of cirrhosis.

- **Ledipasvir-Sofosbuvir** *(NIAID ERADICATE)*: This phase 2 trial investigated the open-label use of ledipasvir-sofosbuvir for 12 weeks in 50 treatment-naïve adults with HCV (genotype 1) and HIV coinfection. Among the 50 participants enrolled, 13 were not taking antiretroviral therapy and 37 were receiving antiretroviral therapy (the antiretroviral medications that were allowed included tenofovir DF-emtricitabine, efavirenz, and rilpivirine). Overall, 98% (49 of
50) of the participants achieved an SVR12.[33]

- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir plus Ribavirin** (TURQUOISE-I): This open-label study randomized treatment-naïve and treatment-experienced adults with chronic HCV genotype 1 and HIV coinfection to receive a 12- or 24-week course of ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin.[26] Participants were required to have a CD4 count of at least 200 cells/mm$^3$ (or CD4% greater than 13) and an HIV RNA level less than 40 copies/mL while receiving an atazanavir- or raltegravir-based regimen. Enrollment included individuals with compensated cirrhosis (Child-Turcotte-Pugh class A) and those with prior treatment with peginterferon plus ribavirin. The SVR12 rates were 94% (29 of 31) in the 12-week group and 91% (29 of 32) in the 24-week group.

- **Sofosbuvir-Velpatasvir** (ASTRAL-5): The ASTRAL-5 study was a single-arm, open-label, phase 3 trial of sofosbuvir-velpatasvir for 12 weeks in adults with HCV and HIV coinfection.[27] The study enrolled 106 individuals with HCV genotype 1, 2, 3, 4, or 6; among those enrolled, 18% had compensated cirrhosis and 29% were treatment-experienced.[27] The mean CD4 count was 583 cells/mm$^3$ and all participants had suppressed HIV RNA levels. A variety of antiretroviral regimens, including regimens that contained tenofovir DF and/or boosting agents (cobicistat or ritonavir), were permitted. The overall SVR12 rate was 95%; two viral relapses occurred, both in persons with genotype 1a HCV; no participants experienced HIV viral rebound during HCV treatment.[27] The presence of cirrhosis or treatment experience did not appear to influence treatment response. Creatinine clearance was lower among participants taking both tenofovir DF and a boosting agent, but the creatinine clearance remained relatively stable over time in all groups.[27]
Recommended HCV Treatment in Persons with HIV Coinfection

AASLD-IDSA HCV Guidance

The American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance addresses treatment of persons with HCV and HIV coinfection in detail.[22] The AASLD-IDSA HCV Guidance recommends using the same general approach for treating HCV in persons with HCV-HIV coinfection as with HCV monoinfection, but notes the importance of recognizing and managing potential drug interactions between HCV medications and HIV antiretroviral medications.[22] In most instances, the recommended HCV treatment regimens are the same persons with HCV monoinfection as in those with HCV-HIV coinfection. One exception is the 8-week regimen of ledipasvir-sofosbuvir, which can be considered for treatment of a selected persons with HCV genotype 1 monoinfection, but should not be used to treat HCV genotype 1 in persons with HIV-HCV coinfection.[22] As with the treatment of persons with HCV monoinfection, the major factors in selecting a regimen to treat HCV in persons with HIV coinfection include HCV genotype, prior treatment experience, presence of cirrhosis, and potential drug interactions with HIV antiretroviral medications.
Treating HIV in Persons with HCV Coinfection

The HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV emphasizes the following key points on treating HIV with antiretroviral therapy for persons with HIV and HCV coinfection:[34]

- Antiretroviral therapy to treat HIV may slow the progression of HCV-related liver disease and reduce the risk of liver-related morbidity.
- For all persons with HIV and HCV coinfection, antiretroviral therapy should be initiated, regardless of the CD4 cell count and fibrosis stage.
- If treatment for both HIV and HCV is indicated, the selected treatment regimens should consider potential drug interactions and overlapping toxicities.
- For individuals living with HIV who have a CD4 counts less than 200 cells/mm$^3$, it may be advisable to first initiate antiretroviral therapy and defer HCV therapy until the person is stable on antiretroviral therapy. It should be noted that the preponderance of clinical trial data on the efficacy of HCV therapy derive largely from patients with suppressed HIV RNA levels on antiretroviral therapy with CD4 counts greater than 200 cells/mm$^3$.
- Antiretroviral therapy-induced liver injury occurs more commonly in persons with HIV and HCV coinfection than in persons with HIV monoinfection.
Drug Interactions with HIV-HCV Coinfection Treatment

Most persons with HIV infection are taking multidrug antiretroviral therapy, which may pose a problem with drug interactions when initiating HCV treatment. For resources on drug interactions that may occur with HIV antiretroviral medications and HCV treatment medications, access the following sites (1) the HHS Adult and Adolescent Antiretroviral Therapy Guidelines Drug-Drug Interactions section, (2) the AASLD-IDSA HCV Guidance Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs tables, (3) the UCSF Center for HIV Information Database of Antiretroviral Drug Interactions tables, and (4) the Liverpool HEP Drug Interactions and HIV Drug Interactions tables. The following provides key points related to potential drug interactions for between HCV medications (DAAs and ribavirin) and HIV antiretroviral medications.

- **Daclatasvir**: The NS5A inhibitor daclatasvir is a substrate of CYP3A. When daclatasvir is given with a CYP3A inhibitor, the levels of daclatasvir can increase, particularly with strong inhibitors of CYP3A. The dose of daclatasvir should therefore be reduced to 30 mg when used with either cobicistat- or ritonavir-boosted atazanavir or with cobicistat-boosted elvitegravir. In contrast, when used with efavirenz, nevirapine, or etravirine, which are CYP3A inducers, the dose of daclatasvir should be increased to 90 mg daily.

- **Elbasvir-Grazoprevir**: Grazoprevir is a substrate of the OATP1B1/3 transporters and therefore contraindicated for use with OATP1B1/3 inhibitors such as the HIV protease inhibitors or cobicistat-containing regimens that can increase grazoprevir drug levels and the risk of hepatotoxicity. Both elbasvir and grazoprevir are metabolized by the CYP3A levels and thus levels may decrease if given with CYP3A inducers, such as efavirenz and etravirine. Coadministration of elbasvir-grazoprevir is not recommended with protease inhibitors, efavirenz, etravirine, or any cobicistat-containing regimen.

- **Glecaprevir-Pibrentasvir**: Glecaprevir is a substrate of OATP1B1/3, P-gp and BRCP and inhibitors of these transporters, specifically the HIV protease inhibitors atazanavir, lopinavir or ritonavir can increase levels of glecaprevir. In addition, use of atazanavir with glecaprevir-pibrentasvir has been associated with increased risk of ALT elevation. Cobicistat-containing regimens may also do so but to a lesser extent; monitoring for hepatotoxicity is advised. Coadministration of glecaprevir-pibrentasvir with inducers of CYP3A, such as efavirenz or etravirine may result in lower plasma concentrations of glecaprevir and pibrentasvir. Glecaprevir-pibrentasvir is contraindicated for use with atazanavir. In addition, glecaprevir-pibrentasvir is not recommended for coadministration with darunavir, lopinavir, ritonavir, efavirenz, or etravirine.

- **Ledipasvir-Sofosbuvir**: The NS5A inhibitor ledipasvir is not metabolized by the cytochrome p450 system, but is both a substrate and an inhibitor of p-glycoprotein and BCRP transporters. Ledipasvir increases tenofovir AUC levels by 40 to 98% when concomitantly given with tenofovir DF and either rilpivirine or efavirenz. Concurrent use of ledipasvir with tenofovir DF and an HIV protease inhibitor (or cobicistat) has not been adequately studied, but there is concern that tenofovir levels may increase substantially with this combination. Because of this concern and lack of data, the use of ledipasvir with the combination of tenofovir DF and cobicistat- or ritonavir-boosted HIV protease inhibitors should, if possible, be avoided. For similar reasons, ledipasvir-sofosbuvir should not be used with cobicistat, elvitegravir, or tipranavir. Monitoring for tenofovir DF nephrotoxicity or switching to tenofovir alafenamide should be considered. Ledipasvir-sofosbuvir should not be used in persons with HIV infection on tenofovir DF if the baseline creatinine clearance is less than 60 mL/min. Ledipasvir does not have significant drug interactions with tenofovir alafenamide.

- **Ombitasvir-Paritaprevir-Ritonavir**: The major concern for drug interaction with this regimen is the cytochrome p450 enzyme inhibition generated by ritonavir. Because the ritonavir has activity against HIV, the patient should ideally be suppressed and on antiretroviral therapy when using this DAA combination. This combination regimen should not be used with cobicistat, efavirenz, rilpivirine, darunavir, tipranavir, or lopinavir-ritonavir. It has been shown to be compatible with atazanavir however; patients who are on cobicistat or ritonavir boosting with atazanavir should have these components discontinued prior to
concurrent use with ombitasvir-paritaprevir-ritonavir.

- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir**: The key drug interaction issue with this regimen is the inhibition of cytochrome p450 enzymes by ritonavir. Because the ritonavir has activity against HIV, the patient should ideally be suppressed and on antiretroviral therapy when using this DAA combination. This combination regimen should not be used with cobicistat, efavirenz, etravirine, rilpivirine, darunavir, tipranavir, or lopinavir-ritonavir. It has been shown to be compatible with atazanavir however; patients who are on cobicistat or ritonavir boosting with atazanavir should have these components discontinued prior to concurrent use with ombitasvir-paritaprevir-ritonavir.

- **Ribavirin**: Significant and serious toxicities can occur with the simultaneous use of ribavirin and certain HIV nucleoside reverse transcriptase inhibitors. The use of ribavirin with didanosine is strictly contraindicated due to a marked increase in intracellular didanosine levels, which may cause hepatic failure, pancreatitis, and lactic acidosis. This can also occur with stavudine or zidovudine. Thus, simultaneous use of ribavirin with either didanosine, stavudine, or zidovudine should be avoided. In addition, concurrent use of ribavirin and zidovudine should also be avoided because of additive hematologic toxicity and increased risk of severe anemia with this combination.

- **Simeprevir**: This NS34A HCV protease inhibitor has complex interactions with antiretroviral medications because it is a substrate and an inhibitor of CYP3A4 and p-glycoprotein. In addition, simeprevir inhibits the OATP1B1/3 drug transporter. Simeprevir should not be used concomitantly with any of the following medications: efavirenz, etravirine, nevirapine, any HIV protease inhibitors, or any regimen that contains cobicistat. Simeprevir can be used with nucleos(t)ide reverse transcriptase inhibitors, rilpivirine, dolutegravir, and raltegravir; if used with maraviroc, the dose of maraviroc should be decreased to 150 mg twice daily.

- **Sofosbuvir**: This NS5B polymerase inhibitor is rapidly converted to a dominant circulating metabolite (GS-331007). Sofosbuvir is not metabolized by the cytochrome p450 system, but is a substrate of p-glycoprotein. The only significant interaction with antiretroviral medications occurs with the p-glycoprotein inducer tipranavir, which may decrease levels of sofosbuvir and the GS-331007 metabolite. Accordingly sofosbuvir should not be used concomitantly with tipranavir, but it can be used with all other antiretrovirals.

- **Sofosbuvir-Velpatasvir**: Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 have the potential to decrease plasma concentrations of sofosbuvir and/or velpatasvir. For this reason, efavirenz and etravirine, as well as tipranavir, are contraindicated for concurrent use. Velpatasvir, when given with tenofovir DF can increase tenofovir levels so caution is advised when using this combination, especially in persons taking additional medications that may increase tenofovir levels or in persons who have an increased risk for nephrotoxicity. An increase in tenofovir levels can occur with coadministration of sofosbuvir-velpatasvir and tenofovir alafenamide, although to a lesser extent than with tenofovir DF.

- **Sofosbuvir-Velpatasvir-Voxilaprevir**: Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 have the potential to decrease plasma concentrations of sofosbuvir and/or velpatasvir. Therefore, efavirenz, etravirine, and tipranavir are not recommended for concurrent use with sofosbuvir-velpatasvir-voxilaprevir. In addition, atazanavir and lopinavir are not recommended for use with sofosbuvir-velpatasvir-voxilaprevir. The same concerns around tenofovir DF and velpatasvir discussed above should be considered when using this combination.
Summary Points

- In persons with chronic HCV, coinfection with HIV accelerates the progression of hepatic fibrosis. Therefore, treatment of both HIV and HCV should have high priority in persons with HIV-HCV coinfection.
- The availability of highly effective, convenient, and safe DAA regimens has changed the HCV treatment landscape for persons with HIV-HCV coinfection. Multiple studies using DAA HCV treatment regimens have demonstrated comparable SVR12 rates in persons with HIV-HCV coinfection as in those with HCV monoinfection.
- The AASLD-IDSA HCV Guidance recommends using the same HCV treatment approach for persons with HIV-HCV coinfection as with HCV monoinfection, except the 8-week ledipasvir-sofosbuvir regimen is not an option in persons with HIV-HCV coinfection.
- Special consideration should be given to monitoring and managing HIV antiretroviral and HCV DAA drug interactions.
- Antiretroviral therapy may slow liver disease progression in persons with HIV-HCV coinfection and should therefore be considered for all persons with HIV-HCV coinfection, regardless of CD4 cell count.
- For persons with HIV-HCV coinfection and a CD4 cell count less than 200 cells/mm$^3$, it may be advisable to initiate HIV antiretroviral therapy first and wait for stabilization of the HIV infection prior to initiating HCV therapy.
Citations


22. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Unique populations: patients with HIV/HCV coinfection.


European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2015. [EASL]


Piroth L, Paniez H, Taburet AM, et al. High Cure Rate With 24 Weeks of Daclatasvir-Based


Figures

Figure 1 Progression to Cirrhosis in Patients with HCV Monoinfection and HIV-HCV Coinfection

This graph shows accelerated progression to cirrhosis in patients with HIV-HCV coinfection when compared with those with HCV monoinfection.

Figure 2 Summary Table of HIV-HCV Coinfection Studies using Peginterferon plus Ribavirin


### Key Studies using Peginterferon + Ribavirin to Treat HCV with HIV Coinfection

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>SVR 24 All</th>
<th>GT1 +/- GT4</th>
<th>GT2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ACTG 5701</td>
<td>PR x 48 weeks</td>
<td>18/66 (27%)</td>
<td>7/51 (14%)</td>
<td>11/15 (73%)</td>
</tr>
<tr>
<td>2 APRICOT</td>
<td>PR x 48 weeks</td>
<td>116/289 (40%)</td>
<td>51/176 (29%)</td>
<td>59/95 (62%)</td>
</tr>
<tr>
<td>3 LAGUNO</td>
<td>PR x 24-48 weeks</td>
<td>42/95 (44%)</td>
<td>12/32 (38%)</td>
<td>10/19 (53%)</td>
</tr>
<tr>
<td>4 RIBAVIC</td>
<td>PR x 48 weeks</td>
<td>56/205 (27%)</td>
<td>21/125* (17%)</td>
<td>35/80‡ (44%)</td>
</tr>
<tr>
<td>5 PRESCO</td>
<td>PR x 48-72 weeks</td>
<td>193/389 (50%)</td>
<td>68/191 (36%)</td>
<td>110/152 (72%)</td>
</tr>
</tbody>
</table>

* includes 26 patients with GT4
‡ includes 2 patients with GT5
Figure 3 Key HIV-HCV Coinfection Treatment Studies using Peginterferon plus Ribavirin

Source
### SVR Rates with GT 1 HCV-HIV Coinfection and HCV Monoinfection

<table>
<thead>
<tr>
<th>Regimen (12 weeks)</th>
<th>Genotype 1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV-HIV Coinfection</td>
<td>HCV Monoinfection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study</td>
<td>SVR</td>
<td>Study</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir</td>
<td>ALLY-2</td>
<td>97%</td>
<td>AI444040</td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir</td>
<td>ION-4</td>
<td>96%</td>
<td>ION-1</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir</td>
<td>TURQUOISE-I</td>
<td>94%</td>
<td>PEARL-III, IV</td>
</tr>
<tr>
<td>Elbasvir-Grazoprevir</td>
<td>C-EDGE Coinfection</td>
<td>95%</td>
<td>C-EDGE TN</td>
</tr>
<tr>
<td>Glecaprevir-Pibrentasvir</td>
<td>EXPEDITION-2</td>
<td>98%</td>
<td>ENDURANCE-1</td>
</tr>
<tr>
<td>Sofosbuvir-Velpatasvir</td>
<td>ASTRAL-5</td>
<td>95%</td>
<td>ASTRAL-1</td>
</tr>
</tbody>
</table>

**Figure 4 SVR Rates in Treatment-Naïve Adults with HIV-HCV Coinfection versus HCV Monoinfection**