JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000001488

High need to switch cART or co-medication with the initiation of DAAs in elderly HIV/HCV co-infected patients

Short title: DDIs in HIV/HCV infected patients

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Reprints: 0

Presented: Data are not presented previously.

Conflicts of Interest and Source of Funding

E.J. Smolders, C. Smit, C.T.M.M. de Kanter and A.S.M. Dofferhoff declare that they have no conflicts of interest that are directly relevant to the content of this manuscript.

J.E. Arends joins advisory boards of Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, ViiV Healthcare and Merck. He received sponsorship of Bristol-Myers Squibb, ViiV Healthcare, Abbvie, and Merck.

K. Brinkman joins advisory board of Gilead Sciences, Bristol-Myers Squibb, Janssen, Abbvie, ViiV Healthcare, and Roche.

B. Rijnders received research grants from MSD and Gilead Sciences, travel grants form ViiV Healthcare, MSD, Bristol-Myers Squibb, Gilead Sciences, and Janssen-Cilag. He received speakers fee from Bristol-Myers Squibb, Gilead Sciences, and Janssen-Cilag en personal fees from Bristol-Myers Squibb, Gilead Sciences, and Janssen-Cilag.

M. van der Valk joins advisory boards of Abbvie, Bristol-Myers Squibb, Gilead, Janssen, ViiV Healthcare and Merck. He received sponsorship and research grants of Gilead, Janssen and Merck.

P. Reiss through his institution received independent scientific grant support, unrelated to the content of this manuscript, from Gilead Sciences Sciences, Janssen Pharmaceuticals Inc, Merck & Co, Bristol-Myers Squibb and ViiV Healthcare; he has served on a scientific advisory board for Gilead Sciences and a data safety monitoring committee for Janssen Pharmaceuticals Inc; he chaired a scientific symposium by ViiV Healthcare, for which his institution has received remuneration.

D.M. Burger joins advisory boards of Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, ViiV Healthcare and Merck. He received sponsorship and research grants of Bristol-Myers Squibb, Janssen Pharmaceuticals, ViiV Healthcare and Merck.

Funding

No funding was received for this project.

Abstract

Backgroud

To describe the use of non-antiretroviral co-medication and combination antiretroviral therapy (cART) in HIV/hepatitis C virus (HCV) co-infected patients, and to predict the potential for drug-drug interactions (DDIs) with direct-acting antivirals (DAAs) against HCV.

Methods

This is a retrospective, cross-sectional study, using the Dutch nationwide ATHENA observational HIV cohort database. All patients with a known HIV/HCV co-infection on 1 January 2015 were included. Co-medication and cART registered in the database were listed. The potential for DDIs between DAAs and co-medication/cART were predicted, using http://hep-druginteractions.org. DDIs were categorized as: (1) no clinically relevant DDI; (2) possible DDI; (3) contra-indication; or (4) no information available.

Results

We included 777 patients of whom 488 (63%) used non-antiretroviral co-medication. At risk for a category 2/3 DDI with non-antiretroviral co-medications were 299 patients (38%). Most DDIs were predicted with paritaprevir/ritonavir, ombitasvir ± dasabuvir (47% of the drugs) and least with grazoprevir/elbasvir (11% of the drugs).

Concerning cART, daclatasvir/sofosbuvir is the most favourable combination as no cART is contra-indicated with this combination. In genotype 1/4 patients grazoprevir/elbasvir is least favourable as 75% of the patients must alter their cART.

Conclusions

This study showed that co-medication use in the aging HIV/HCV population is frequent and diverse. There is a high potential for DDIs between DAAs and co-medication/cART.

Keywords: cART, co-medication, direct-acting antivirals, drug–drug interactions, hepatitis C, HIV.

1. Introduction

Due to shared routes of transmission and overlapping at risk populations, HIV patients are commonly co-infected with hepatitis C virus (HCV). It is estimated that, worldwide, 2.3 million people live with an HIV/HCV co-infection[1]. In the Netherlands 12% of the HIV-infected patients tested were positive for HCV antibody or HCV RNA. The majority of these patients are men who have sex with men (46%) or current/former drug users (31%) [2].

Both HIV (combination antiretroviral therapy [cART]) and HCV (direct-acting antivirals [DAAs]) treatments can be victims (substrates) and/or perpetrators (cause) of drug–drug interactions (DDIs)[3]. For example, nevirapine is a strong inducer of cytochrome P450 (CYP) 3A4, and therefore interacts with velpatasvir (CYP3A4 substrate)[4]. On the other hand, the combination of ombitasvir, paritaprevir/ritonavir ± dasabuvir (PrO±D), strongly inhibits CYP3A4, causing increased rilpivirine (CYP3A4 substrate) levels[5].

These examples demonstrate that DDIs could be a potential problem in HIV/HCV co-infected patients. So far, this has been studied mainly focusing on cART/DAA interactions[6-9]. However, treatment of co-infected patients is complicated in the aging HIV population, as these patients often suffer from somatic or psychiatric co-morbidities for which co-medication is prescribed. Thus, besides cART, management of DDIs in HIV/HCV co-infected patients should also focus on interactions between DAAs and these co-medications. Furthermore, earlier publications in general did not include evaluations of the most modern DAAs, such as velpatasvir and grazoprevir/elbasvir, which are now recommended first line agents.

We aimed to identify the use of co-medication and cART and predicted DDIs of these medications with all currently available DAAs in a Dutch nationwide HIV/HCV co-infected cohort.

2. Methods

This retrospective, cross-sectional study, used the ATHENA database managed by the HIV monitoring Foundation (http://www.hiv-monitoring.nl). This is a Dutch, nationwide registry in which all HIV-infected patients in care who did not opt-out are registered. All patients with a known HIV/HCV co-infection on 1 January 2015 were included (HCV RNA positive). These patients were not treated with DAAs before, as these drugs became available in the Netherlands on 1 January 2015. The included patients represent the total population of patients which could potentially be treated with DAAs and co-medication and cART were thus not altered because of DDIs with DAAs. The reported co-medication and cART was used to predict DDIs using the database of the University of Liverpool (http://hep-druginteractions.org; September 2016)

This analysis was done in four steps: 1) Identification of co-medication used in the cohort; 2) prediction of DDIs between co-medication and DAAs; 3) Identification of cART used in the cohort; 4) prediction of DDIs between cART and DAAs.

2.1 Identification of co-medication

All non-antiretroviral co-medication was extracted from the database, from which a list was compiled of all unique co-medications.

2.2 Prediction of DDIs between co-medication and DAAs

The list (2.1) of co-medications was used for the prediction of DDIs. Each drug was cross-checked if DDIs exist with one of the DAA-regimens. We included all DAA-regimens recommended in Dutch guidelines in November 2016[10]. DDIs were categorized as: (1) no clinically relevant DDI expected; (2) possible DDI expected, i.e. monitor the patient or alter drug dosage/timing; (3) contra-indication, do

not co-administer; or (4) no information available in the Liverpool database. Category 2 and 3 DDIs were defined as clinically relevant.

We reported per DAA-regimen the number of co-medications with a potential DDI.

After determination of the DDIs between the unique co-medications and DAA-regimens, we assessed the number of patients, per genotype, at risk for a clinically relevant DDI. We counted the patients that had at least one predicted DDI with any of the DAA-regimens. Dutch recommendations of November 2016 were used to determine which DAA-regimen can be used per genotype[10]. Patients with an unknown HCV genotype were analyzed with pan-genotypic regimens: sofosbuvir+daclatasvir and sofosbuvir+velpatasvir. We reported per genotype, the frequency of patients at risk for a DDI.

In addition, patients with DDIs were counted for those (a) with or without cirrhosis, and those (b) <60 or >60 years. Cirrhosis (METAVIR F3/F4) was defined using a pathology or Fibroscan report (stiffness >9.5kPa).

2.3 Identification of cART

Antiretroviral drugs registered in the database were extracted and a list of antiretroviral drugs per patient was compiled.

2.4 Prediction of DDIs between cART and DAAs

The list from 2.3 was used for the prediction of DDIs. To simplify the analysis only patients with a double nucleoside reverse transcriptase inhibitors (NRTI) backbone and 1 additional drug were included. These additional drugs can be a (boosted) protease inhibitor (PI), (boosted) integrase inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). These additional drugs are usually causing DDIs and therefore used in this analysis. Patients with other regimens were excluded. Per genotype and DAA-regimen the number of patients at risk for a DDI was reported.

Lastly, the patients using tenofovir disoproxil fumarate (TDF) and boosted PIs were identified. This combination interacts with ledipasvir and velpatasvir causing possible renal toxicity. It is therefore recommended to discontinue TDF or the boosted PI prior to ledipasvir and velpatasvir therapy (category 2).

Analyses were performed using IBM SPSS Statistics 20.

3. Results

The ATHENA database contained data on 777 HIV/HCV co-infected patients known to be in care on 1 January 2015. The majority of these patients were male (666; 86%). The median (range) age was 49.3 (23-80) years; 689 patients were <60 years and 88 were ≥60 years. METAVIR score F0/F1/F2 was reported for 438 (56%) patients and F3/F4 for 181 (23%) patients (158 unknown). Genotype 1 and 4 were most prevalent, in 495 (64%) and 139 (18%) patients, respectively (supplementary Table 1 http://links.lww.com/QAI/B59).

3.1 Identification of co-medication

An overview of co-medication use is presented in Figure 1, showing that 488 patients used 156 unique non-antiretroviral co-medications. Medication use varied from 1 to 14 prescriptions per patient (excluding cART), in total 1,245 prescriptions were reported. Most frequently used medications were drugs for opioid dependence (138; 11%), proton pump inhibitors (110; 9%), calcium supplements (77; 6%), selective serotonin reuptake inhibitors (56; 4%), platelet aggregation inhibitors (53; 4%), Vitamin D (46; 4%), and statins (45; 4%). In Supplementary table 2 http://links.lww.com/QAI/B59 these drug classes are broken down to the drugs that were prescribed at least to 10 patients (single molecules).

3.2 Prediction of DDIs between co-medications and DAAs

Grazoprevir/elbasvir and sofosbuvir/velpatasvir had the lowest number of predicted DDIs with the 156 co-medications. PrO±D and sofosbuvir/simeprevir account for the highest number of predicted

category 2 and 3 interactions with the used co-medication. Overall, the number of truly contra-indicated drugs is low, with a maximum of 10 drugs for PrO±D. We were not able to predict potential DDIs of 23 drugs (category 4), as these drugs were unavailable in the Liverpool database (Figure 1).

Converting the number of drugs (156) to the number of patients with a category 2 or 3 DDI with any of the DAAs, we found that 299 patients were at risk. This concerns 205 (41%) genotype 1, 34 (36%) genotype 2/3, 54 (39%) genotype 4, and 6 (12%) patients with an unknown genotype. Furthermore, 269 (40%) patients <60 years and 55 (77%) patients ≥60 years were at risk for a category 2 or 3 DDI with any of the DAA-regimens. Similarly, 147 (34%) and 100 (55%) patients without and with cirrhosis, respectively, were at risk for a DDI.

3.3 Identification of cART

A total of 762 (98%) patients were treated with cART. The NRTI backbone containing TDF+emtricitabine was used by 536 (70%) of patients and 103 (14%) patients used abacavir+lamivudine.

The majority of patients used 1 additional (e.g. PI, INSTI, NNRTI) antiretroviral drug (670; 88%) and 40 (5%) patients used more than 1 additional antiretroviral. Most frequently used additional drugs were NNRTIs (307; 46%), followed by the boosted PIs (247; 37%), and INSTIs (116; 17%). Please note that on the date of evaluation, 1 January 2015, dolutegravir had only been available for 2 months.

3.4 Prediction of DDIs between cART and DAAs

Per genotype, the predicted DDIs per patients are shown (*n* = 669; Figure 2). None of the genotype 1 and 4 patients would have to change their cART when treated with sofosbuvir/daclatasvir. However, the dosage of daclatasvir should be altered depending on some specific cART regimens. Ledipasvir and velpatasvir in combination with sofosbuvir can be safely used with all third additional drugs. However, 199 (31%) genotype 1 or 4 patients used TDF with boosted PIs, which makes it necessary to switch either TDF or the PI. Comparable, in combination with velpatasvir patients infected with all

genotypes using TDF with a boosted PI (*n* = 231; 29%), are recommended to switch either TDF or the PI.

Grazoprevir/elbasvir causes the most category 3 DDIs, making a change in DAA or cART regimen necessary. Other regimens with category 3 interactions were sofosbuvir with velpatasvir/simeprevir and PrO±D. For patients with genotype 2/3 or an unknown genotype it is shown that sofosbuvir/daclatasvir can be used without cART switch.

4. Discussion

This cohort represents all Dutch HIV/HCV co-infected patients in care in the Netherlands who might be treated with the novel DAAs. Most commonly used co-medications reflect the characteristics of the HIV/HCV patient population, such as the drugs used for opioid dependence[2]. Other drug classes in the top 5 are comparable with HCV mono-infected patients in The Netherlands[11] and represent the aging HIV population with an increasing number of co-morbidities. This is supported by our subgroup analysis where patients ≥60 years had a higher risk of DDIs than patients <60 years. Similarly, patients with cirrhosis had a higher predicted risk of DDIs than patients without cirrhosis. This is comparable with findings in HCV mono-infected patients[12].

PrO±D and sofosbuvir/simeprevir have the highest number of predicted DDIs with non-antiretroviral co-medication, which is in line with previous studies[6,8,9]. Both combinations contain inhibitors of CYP3A4 (i.e. ritonavir, simeprevir), which is the main drug-metabolizing enzyme[5,13]. However, we must mention that in daily practice these regimens are infrequently used, because of the e.g. the DDIs and protease inhibitor related side effects.

Grazoprevir/elbasvir had the lowest number of DDIs with co-medication, because they have minimal influence on drug-enzymes and transporters[14]. One should notice that grazoprevir is a mild inhibitor of CYP3A4. Therefore, we recommend being careful with CYP3A4 substrates with a narrow therapeutic range. However, it remains unclear whether these DDIs are clinically relevant.

Sofosbuvir/daclatasvir can be easily combined with cART, because of the possibility of a dose adaptation and no contra-indicated cART regimens. Despite the fact that ledipasvir has only category 2 DDIs, it is less favourable, because ledipasvir is not recommended with the combination of a boosted PI and TDF, an issue that would require a switch in cART in 31% of patients. This interaction, as well as the interaction with velpatasvir (29%), can also be avoided when switching from TDF to tenofovir alafenamide (TAF). TAF plasma concentrations are not affected by ledipasvir[15].

In most countries, the separate agents daclatasvir and sofosbuvir are in general a more expensive DAA-regimen compared with the fixed-dose combinations with velpatasvir and ledipasvir and therefore prescribed in a lesser extent. In the Netherlands, the prices of DAAs are unknown and therefore not a criteria for selecting a DAA-regimen [10].

It is striking that grazoprevir/elbasvir has the lowest number of interactions with non-antiretroviral co-medication, but this combination has the highest number of DDIs with cART. Grazoprevir/elbasvir (and simeprevir) is contra-indicated with all boosted PIs, NNRTIs (except rilpivirine) and elvitegravir/cobicistat; this makes it an unfavourable combination in this co-infected population because almost all patients would need to alter their cART regimen, if they are not already on raltegravir or dolutegravir. NNRTIs and PIs are most frequently used in our cohort, but with the introduction of dolutegravir, the use of NNRTIs and PIs decreased[2].

A limitation of the analysis is that patients with the most complicated cART regimens (e.g. >1 additional drug, no NNRTI backbone) were excluded from the analysis presented in Figure 2. These patients are probably the most difficult to treat HIV patients, because they have deviating cART regimens, and therefore, switching cART is probably not an option in these cases (e.g. resistance, toxicity). For these patients, the treatment strategy is to use a DAA-regimen with least number of (possible) drug-interactions.

Lastly, we must comment that the majority of the DDIs which are discussed in this paper are only studied in healthy volunteers and not in HIV/HCV co-infected patients. These drug interactions studies in healthy volunteers give a good indication of the direction of the DDI, however, as healthy

volunteers substantially differ from HIV/HCV co-infected the magnitude of the DDIs could differ as, for example, the exposure to DAAs and antiretroviral drugs is probably different in healthy volunteers and HIV/HCV patients[16].

Concluding, this study showed that co-medication use in the aging HIV/HCV population is frequent and diverse and that there is a high potential of DDIs between DAAs plus co-medication/cART. Combining the results from our analysis, from the perspective of potential DDIs with co-medication and/or cART, the most favourable regimen seems to be sofosbuvir/daclatasvir.

Ethics Statement

At initiation, the ATHENA observational cohort was approved by the institutional review board of all participating centers. It has subsequently become integral part of HIV care and includes pseudonymised data and stored plasma samples from HIV-infected patients living in the Netherlands and receiving care in one of the designated HIV treatment centers. Patients can opt-out after being informed by their treating physician of the purpose of collection of data and samples. Data from patients who opt-out are not included in the ATHENA database. Pseudonymised data may be used for scientific purposes without further review. Patients are informed that in case of future requests for use of stored plasma samples for scientific research they will be asked for prior consent by their treating HIV physician. Data are pseudonymised before being provided to investigators**.** For the purpose of our analysis only existing data have been used and therefore no additional review or consent has been necessary.

Acknowledgements

The ATHENA database is maintained by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment.

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Figure 1: Flow chart of the study including the number of predicted drug-drug interactions with various DAA-regimens and co-medication. A total of 1,245 prescriptions were available for 488 patients. These prescriptions contained 156 unique drugs, which were used for the analysis.

The number of drugs for each category are shown in parentheses. Category 1, 2, 3 and 4, respectively.

DDI, drug–drug interaction; HCV, hepatitis C virus; PrOD, ombitasvir, paritaprevir, ritonavir with dasabuvir; PrO, ombitasvir, paritaprevir, ritonavir; SOF + SIM, sofosbuvir and simeprevir; SOF + LED, sofosbuvir and ledipasvir; SOF + DAC, sofosbuvir and daclatasvir; SOF + VEL, sofosbuvir and velpatasvir, GRV + EBV: grazoprevir and elbasvir.

Figure 2: The number of patients predicted to have a drug interaction between cART and the various combinations of direct-acting antivirals shown per genotype.

Only patients with one additional (third) drug are included in this analysis (*n*=670).

Genotype 6 is excluded from this analysis, as only one patient was listed with genotype 6 (*n*=669).

Category 2 30 mg: reduce the daclatasvir dose to 30 mg.

Category 2 90 mg: increase the daclatasvir dose to 90 mg.

PrOD, ombitasvir, paritaprevir, ritonavir with dasabuvir; PrO, ombitasvir, paritaprevir, ritonavir; SOF + SIM, sofosbuvir and simeprevir; SOF + LED, sofosbuvir and ledipasvir; SOF + DAC, sofosbuvir and daclatasvir; SOF + VEL, sofosbuvir and velpatasvir; GRV + EBV, grazoprevir and elbasvir.

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