1. ABSTRACT

Title

Impact of single tablet regimens (STR) on adherence and prescription errors – how big an issue and how relevant, in both clinical and economic terms

Keywords

Retrospective Study, Adherence, STR, Non-STR, Prescription errors, Atripla , Eviplera, Stribild.

Rationale and background

HIV-1 infection is a life-threatening and serious disease that is of major public health significance, with approximately 36.7 million people infected worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. Standard of care for the treatment of HIV-1infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase cluster determinant 4 (CD4) cell counts, and stop disease progression. For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consists of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI) {British HIV Association 2013, Department for Health and Human Services (DHHS) 2015, European AIDS Clinical Society (EACS) 2014}. Virologically suppressed, HIV-infected patients may switch from their current regimen because of safety or tolerability concerns, or for regimen simplification.

Successful treatment outcomes for HIV infected patients taking ART have been hampered by complicated regimens and high pill burden potentially leading to inadequate adherence, drug-drug interactions, and frequent short- and long-term adverse effects {Dejesus 2009}. Single tablet regimens (STRs) with their reduced pill burden, low dosing frequency and overall regimen simplification have become an important option for patients with HIV.

Previous studies have shown that inadequate adherence is a critical factor contributing to the development of viral resistance and treatment failures {Gardner 2008a}. Improving adherence to antiretroviral medication will lead to both improved virological suppression rates and overall patient outcomes. The association between adherence to ART and therapeutic success has been demonstrated {Hogg 2000, Kahana 2013, Ready 2010}. Poor adherence has a higher risk of drug failure, viral mutations and development of drug resistance {Friedland 1999, Martin 2008, Nachega 2010, Paterson 2000, Sethi 2003}.

Investigators hypothesize that selective adherence (SA) accounts for a non-negligible portion of overall inadequate adherence (OIA) and that both SA and non-adherence (NA) are clinically and economically relevant. STRs are, by definition, SA-free regimens. Three analyses have appraised this value of STRs suggesting that STRs are associated with higher rates of viral suppression and higher CD4 cell counts {Antinori 2012}, lower probability of hospitalisation and lower annual costs {Antinori 2012, Cohen 2012, Vahlenkamp 1995, Vera 2012, Yokota 1994}.

Medication errors with antiretroviral therapy (ARV) may have serious long-term consequences, including the development of drug resistance, treatment failure, or death {Yehia 2012}. Depending on the source of information, medication error rates related to ART regimens among hospitalised patients reported in the literature, can be as high as 72% {Pettit 2012, Shantsila 2007, Velo 2009}. Of these, prescription errors are a major problem and account for 70% of medication errors that could potentially result in an adverse event {Velo 2009}.

Research question and objectives

The aim of this study was to determine whether STRs, as SA-free regimens, would:

- improve adherence and generate clinical and economic benefits
- prevent prescription errors.

Primary Objective

- To assess the impact of STRs, as compared to non-STRs, on adherence in HIV-1 infected patients.

Secondary Objectives

- To assess the direct effect of STR versus non-STR on
  - virological failure
  - hospitalisation
  - ART plus hospitalisation costs
- To assess the effect of NA and OIA (overall and STR versus non-STR) on
  - virological failure
  - hospitalisation
  - ART plus hospitalisation costs
- To quantify ART prescription errors

Setting

The source population for both parts of this non-interventional study were HIV-1 infected adult patients taking ART, retrospectively recruited from centres in Italy, Portugal, Spain and the UK by investigators that had expertise in the management of HIV infection.

Adherence study

Study design

The population for the adherence component for this study was HIV-1 infected adults who received ART between 1st January 2009 and 31st December 2013 (the observation period). The main study (= adherence study) focused on patient adherence to anti-HRV ART. Adherence was evaluated in a matched retrospective cohort study.

Patient-regimens permitted

Two cohorts were considered: STR (defined as a regimen containing single tablet regimens recommended by the European AIDS Clinical Society (EACS) Version 7.0 October 2013 {European AIDS Clinical Society (EACS) 2013}) and non-STR (defined as a regimen containing multi pill once daily combinations recommended by the European AIDS Clinical Society (EACS) Version 7.0 October 2013 {European AIDS Clinical Society (EACS) 2013}). Stribild was not included in EACS Version 7.0 but was allowed as STR in this study. However, no patient on Stribild was finally identified and recruited for this study.

Subjects and study size

STR and non-STR subjects were defined, for subject selection purposes, according to the type of regimen they were on by 31st December 2013. Once subjects were selected, the relevant unit of analysis was the patient-regimen and both matching and the statistical analysis were performed at the patient-regimen level. In order to maximize homogeneity between the two cohorts and reduce the impact of treatment-selection bias, a propensity score matching (PSM) approach was applied at the patient-regimen level. Data was collected on patient-regimens that were given for at least 90 days at any time during the observation period. All data in the eCRF was de-identified to maintain subject confidentiality. A study number was assigned for each subject and patient-regimen.

The sample size needed to achieve a power of 80% for detecting a difference of 0.02 in the proportion of patients with adherence > 90% between the two cohorts resulted in a post Propensity Score Matching (PSM) of 1030 pairs of patient-regimens. Based on preliminary evaluation, an average of 80 subjects in the STR cohort and 90 subjects in the non-STR cohort were calculated to be needed per centre to ensure that the overall size of 2060 patient-regimens would be reached.

Data sources

The main source of data was the subject clinical records. Centres participating in the Adherence study must have had complete history (within the observation period) of pharmacy refills available electronically in the hospital records.

Pharmacy refill data i.e. medication possession was used to measure adherence based on proportions of days (out of the total regimen duration):

- Adherence was defined as the proportion of days in which the patient did have all of the components of the regimen in his possession.
- NA was defined as the proportion of days in which the patient did not have any of the components of the regimen in his possession.
- SA was defined as the proportion of days in which the patient did not have some (but had other) components of the regimen in his possession. Thus, SA is not possible for STR regimens.
- OIA is the proportion of days the patient did not have any or did not have some (but had other) components of the regimen. Thus OIA=NA+SA. For STRs OIA=NA, as SA is not possible here.

Adherence study – Variables collected

After confirmation of eligibility criteria, investigators collected the following data for each subject selected, based on clinical/pharmacy/prescription records. Each selected subject may have had one or more valid patient-regimens.

Demographics (date of birth, gender, race), baseline characteristics (most likely mode of HIV infection, date of ART initiation, number of virological failures, HIV ribonucleic acid (RNA) and CD4 cell count at ART initiation, CD4 cell count nadir), patient-regimen characteristics (i.e. characteristics with current consumption: illegal drugs dependency, alcohol dependency, smoker, current opioid substitution treatment, mental disorder, Acquired Immune Deficiency Syndrome (AIDS) status, Hepatitis C status), ARV treatment prescription, laboratory parameters, resistance profile (usage of REGA 8.0 algorithm, genotype sensitivity score), inpatient care episodes (date, duration, ICD-9 or ICD-10 for inpatient episode, diagnosis-related group (DRG) code admitting service), ARV treatment pharmacy refills, adverse drug reactions (ADRs) and pregnancy.

Prescription error sub study

Sub study design

A sub study reviewed and quantified prescription errors. Only centres where prescription data was available were included in the prescription errors sub study. ART prescription errors were evaluated by a retrospective review of medication orders during the first 48 hours of hospitalisation for HIV infected adults admitted for any reason to a participating centre between 1st January 2012 and 31st December 2013.

Subjects, study size, patient-regimens permitted and data sources

In this sub study, two cohorts were also considered: STR and non-STR. However, the STRs considered for the sub study were not limited to the EACS v 7.0 recommendations. This was an analytical cross-sectional study that aimed to identify the proportion of hospital episodes in which prescription errors occurred. Data was collected by manual review of subject clinical records and types of error classification were performed by the investigator.

The study aimed to include 40 inpatient care episodes of HIV-1 infected subjects per centre.

For centres participating in the prescription errors sub study, registration of ART errors, in either paper or electronic format, was required.

Variables collected

Individual characteristics (Date of birth, gender, race), inpatient care episodes (date, duration, ICD-9 or ICD-10 for inpatient episode, DRG code admitting service), Prescription errors audit (Type of error: absence/incomplete regimen, incorrect dosage, incorrect schedule, incorrect formulation, duplication of ART therapy, non-recommended drug-drug combinations (ART-ART and AR-non-ART), drug-drug interactions, error resolved), ADRs and pregnancy.

Results

Adherence study

1393 patient regimens were included in the adherence study that matched the EACS v7.0 guidelines and lasted at least 90 days. However, due to missing values 270 (19.4%) regimens were excluded from analyses, resulting in 1123 regimen before PSM matching.

Before applying the PSM approach, significant differences were observed in the two cohorts (Table 1): The non-STR cohort included more patients with confirmed Hepatitis C status at baseline compared to the STR cohort (32.3% versus 19.8%), as well as more patients with controlled mental disorder (12.1% versus 4.9%), fewer male patients (68.1% versus 79.2%), patients with higher HIV RNA levels and a higher number of virological failures. Post matching there were 404 STR and 404 Non-STR records in the adherence study component not showing significant differences in the matching variables.

Eighty two percent of patients taking STRs achieved >90% adherence in contrast to 65.1% of patients on non-STRs. Thus, patients taking STR had 2.5 (95% CI 1.8, 3.5) significantly higher odds of achieving >90% adherence than those taking non-STRs. Similar results were observed for patients achieving >95% adherence.

Comparing the mean percentage of days without some drugs or any drug out of the total days on regimen per study group (OIA) showed that patients taking STRs had a significantly lower OIA (4.9; 95% CI 4.1, 5.7) when compared to patients on non-STRs (9.5; 95% CI 8.4, 10.6); p-value <0.0001.

No other significant results were observed for all secondary endpoints of this study:

- Only 14 patients being suppressed when starting their regimen became unsuppressed while on their study regimen (non-STR [n=5] versus STR [n=9]) resulting in an adjusted odds of becoming unsuppressed of 1.3 (95% CI 0.68-2.4) for STRs. Only the adherence variable was used for adjustment as all other variables were already used in the PSM approach.

- In the group of non-STRs a total of 30 (7.4%) hospitalisations were observed in contrast to 19 (4.7%) for STRs, resulting in an adjusted odds of hospitalisation of 0.85 (95% CI 0.61-1.2) for STRs.

- The combined average monthly ART plus hospitalisation costs were similar for non-STRs (mean 1004.3 Euros, 95% CI 879.2-1129.4) compared to STRs (mean 962.5 Euros, 95% CI 812.0-1113.0).

- The rate of hospitalisation episodes per 1000 regimen month was higher for non-STRs (rate 29.3) compared to STRs (rate 18.1), resulting in an incidence rate ratio of 0.61 (95% CI 0.34-1.1) after adjusting for the adherence level.

- The rate of ADRs per 1000 regimen months was lower for non-STRs (rate 0.006) compared to STRs (rate 0.011), with an incidence rate ratio of 1.8 (95% CI 0.82-3.8) after adjusting for the adherence level.

- Analysis on genotype sensitivity score were not conducted as scores were available in only 10.7% of all regimens.

Although explicitly permitted in the inclusion criteria, no patient on Stribild was identified and recruited for this study.

Prescription error sub study

A total number of 175 hospital episodes were identified with 24 prescription errors. Thus, only limited descriptive analyses were done on this sub study. Out of the 27 and 148 hospital episodes in the STR and non-STR arms respectively, 4 prescription errors (14.8%) were observed in the STR arm and 20 (13.5%) in the non-STR arm.

Discussion

This study demonstrated patients who were taking STRs had significantly higher levels of adherence than patients taking non-STRs. Patients who were prescribed STRs had significantly higher odds of achieving both 90% and 95% adherence levels when compared to patients taking non-STRs. This finding is in line with previous studies examining adherence in patients taking combination therapy {Bangalore 2007}.

Although the study did not reach the recruiting numbers it aimed for (1393 patient regimens included instead of 2060) it did show a significant difference in adherence, potentially due to the fact that difference in the proportion of patients reaching more than 90% adherence was higher

than expected. However, no further significant results were identified, neither in the main study nor in the prescription errors sub study. Thus, the fact that this study was underpowered may have led to issues of generalizability with respect to the majority of the results.

The sub study aimed to include 40 episodes per recruiting centre, resulting in a potential total of 360 prescription episodes from the initially nine participating centres. Although only one centre dropped out, only 48.3% of the targeted prescription error episodes were collected.

Only 4 unique prescription errors (14.8%) were observed in the STR arm and 20 (13.5%) in the non-STR arm. Although there is no proper base for interpretation some of these may have been intentional and driven by factors related to specific patients, such as toxicities or previous resistance. No conclusions can be drawn from the prescription error sub study.

Conclusion

In conclusion this study has shown that patients taking STR based regimens are more likely to adhere to their medication when compared to patients taking non-STR therapies.

However, this study under recruited participants and thus did not show any clinical or economic impact. Therefore there are issues of generalizability with respect to the majority of the results.

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