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CASE REPORT: REASONS FOR NON-ADHERENCE TO ANTIRETROVIRAL THERAPY (ART) IN A RETROVIRAL DISEASE (RVD) PATIENT

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Abstract:

Objective: To report a case of an HIV patient who was not compliant to ART medications, and explain the reasons behind that.

Case Summary: This 36 years old Malay female with 49kg was attended to retroviral disease (RVD) Medication Therapy Adherence Clinic (MTAC) at Hospital Sungai Buloh (HSB) to follow up and refill her antiretroviral therapy (ART) regimen on 20th August 2018. She has been diagnosed with RVD since 2004, but started her highly active antiretroviral therapy (HAART) since 2008 when she visited HSB for the first time. She was given a variety combination of HAART regimens from 2008 until 2018, and developed resistance to some of them due to her poor compliance. ART medications' side effects and number of pills are the main reason to default the medications. Consequently, she has failed the first line regimen, and currently has not had any good treatment regimen with virological suppressions.

Discussion: Treatment adherence is generally regarded as an important factor in achieving optimal outcomes across many disease states; in the treatment of human immunodeficiency virus (HIV), poor adherence to treatment has the potential to impact outcomes on multiple levels. The causes of poor adherence to ART are extremely diverse, and include complexity of therapeutic regimens (eg, pill burden and dosing frequency), and treatment side effects. Treatment approaches, such as the use of fixed-dose combinations of ART agents to reduce dosing complexity, giving symptomatic treatments to treat the side effects, as well as educational interventions, such as medication therapy management initiatives, have been shown to improve adherence to therapy in HIV.

Conclusion: A case of patient, who has failed multiple HAART regimens, was presented and reasons that lead the patient to have poor compliance and developed resistance to certain ART drugs were discussed.

Keywords: HIV, HAART, Non-adherence

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1.0 Introduction:

Numerous effective therapeutic agents for viral suppression in HIV have been developed. Their efficacy, however, requires that patients with HIV be adherent to their prescribed regimens. Effective use of antiretroviral agents requires not only good adherence to therapy on the part of patients but sustained adherence over

time (persistence) if viral suppression is to be successful.[1] For HIV therapeutic regimens in which an un-boosted protease inhibitor is a component, there exists a substantial risk of failed viral suppression with treatment adherence with treatment adherence less than 95 %.[2] High levels of treatment adherence in HIV have been shown to predict better viral suppression outcomes, whereas poor treatment adherence in HIV is associated not only with less effective viral suppression but also with drug resistance and reduced survival.[3,4] The Figure 1 shows the relationship between levels of adherence to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and viral suppression in an observational cohort study involving 2821 adults infected with HIV.

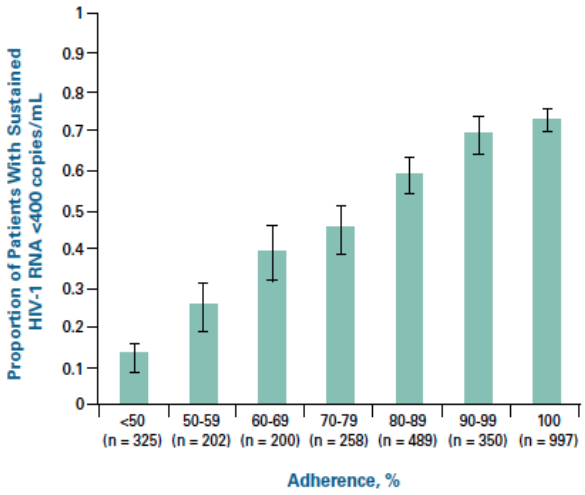

Figure 1 Relationship of adherence to to NNRTIs and viral suppression in 2821 HIV-positive patients[3]

Different classes of antiretroviral therapy (ART) are associated with different thresholds of adherence needed to achieve viral suppression and avoid resistance mutations. For example, highly active antiretroviral therapy (HAART) based around an NNRTI needs a very high level of adherence to limit the risk of resistance mutations. A study by Maggiolo et al found a 4.9% risk of resistance mutations in patients receiving NNRTI-based HAART who dropped below a 75% rate of treatment adherence, while patients treated with HAART with an unboosted protease inhibitor (PI) as its backbone had a very low mutation risk at that level of adherence. Boosted PIs were associated with a mutation risk between unboosted PIs and NNRTIs at the same adherence rate. By comparison, the risk of viral rebound after the cessation of an unboosted PI HAART regime was approximately 5-fold the viral rebound risk observed with an NNRTI-based HAART, while a boosted PI HAART regime had a rebound risk approximately two-thirds greater than NNRTI.[5] The data on integrase inhibitors is much more limited at present, and it remains uncertain where these agents sit on the HAART spectrum with regard to adherence requirements. The causes of poor adherence in HIV treatment are extremely varied (Table 1),[6] including patient challenges related to age, health literacy, psychosocial and neurocognitive issues, and substance abuse, among other factors. Adherence is also impacted by medication-related barriers, such as complexity of regimens and treatment side effects; and healthcare system challenges, such as drug costs and coverage issues, can also reduce the likelihood of a patient taking his or her medications as appropriate. The purpose of this case report is to review the nature and impact of several key adherence-related factors in HIV patient that may leads to poor compliance.

Table 1 Common factors associated with poor treatment adherence to ART

• Low levels of health literacy
• Age-related challenges (eg, polypharmacy, vision loss, cognitive impairment)
• Younger age
• Psychosocial issues (eg, depression, homelessness, low social support, stressful life events, psychosis)
• Nondisclosure of HIV serostatus
• Neurocognitive issues (eg, cognitive impairment, dementia)
• Active (but not history of) substance abuse, particularly for patients who have experienced recent relapse
• Stigma
• Difficulty with taking medication (eg, trouble swallowing pills, daily schedule issues)
• Complex regimens (eg, high pill burden, high-frequency dosing, food requirements)
• Adverse drug effects
• Nonadherence to clinic appointments
• Cost and insurance coverage issues
• Treatment fatigue
ART indicates antiretroviral therapy.

2.0 Case Report:

36 years old Malay female with 49kg was present to retroviral disease (RVD) Medication Therapy Adherence Clinic (MTAC) at Hospital Sungai Buloh (HSB) to follow up and refill her antiretroviral therapy (ART) regimen on 20th August 2018. She has been diagnosed with RVD since 2004, but started her highly active antiretroviral therapy (HAART) since 2008 when she visited HSB for the first time, and was pregnant at that time. She is married and currently working in electrical factory. She denied smoking, drug abuse or consuming alcohol. Mode of HIV transmission is from her husband, heterosexual. Her husband is also following up at HSB. She was afebrile during all

the times she came to RVD MTAC, and her blood pressure was well controlled by fluctuated between 110/68 to 132/78 mmHg. She gave birth on 22/10/2008, and zidovudine was given directly to the baby as prophylaxis to avoid her from getting HIV. Baby is a girl, and regular HIV test has been done to her, and showed negative result so that her daughter did not have RVD yet. This patient antiretroviral therapy (ART) history is as follows:

- Zidovudine (AZT)+Lamivudine (3TC)+Lopinavir/retronavir (LPV/r) were given in 2008 as treatment and prophylaxis to prevent of mother-to-child transmission (PMTCT).
- AZT + 3TC + Nevirapine (NVP) were given in May 2009 (post-delivery).

Patient's HIV RNA viral load (VL) kept increasing gradually from 88 on 2008 to peak up to 10753 on 2010 while T-helper CD4 counts showed slowly increased. This indicated that there was no immunological failure yet, but virological failure was present. Hence, HAART stopped, and 2nd line was initiated.

- Tenofovir (TDF) + Emtricitabine (FTC) {Tenvir Em} + Atazanavir/retronavir (ATV/r) was given on Feb 2011. Retronavir did off after a month, and ATV was out of stock and replaced with LPV/r on March 2011. Next, Tenvir Em + Ritonavir + Atazanavir was given on May 2015 .
- HIV RNA viral load kept increasing ,and there was still no good viral suppression, so HAART regimen switched to Kaletra (LPV/r) + Raltegravir since July 2016-June 2017. Patient claimed that she could not tolerate Kaletra as caused her to have diarrhea.

Resistance test has done and showed that there was high level of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI), and sensitive to Kaletra and Tenvir Em. Another Resistance test did do on May 2018 showed that there was a great resistance to Raltegravir.

- The latest and current HAART regimen includes Tenvir Em + Atazanavir+ Ritonavir.

Throughout all the times, patient was not compliance properly to all the medications. She claimed that Atazanavir pill size is big; Kaletra causes her to have diarrhea and sometimes giddiness. Besides, she claimed that she cannot take at same time many medications. RVD MTAC preceptor stated that this patient still has not had any good treatment regimen with a good virological suppression. It is expected to reach up to the point that no proper treatment can help her condition, and would be given salvage regimen if patient ignores the medications, and did not take her medications strictly on time with a proper adherence. During her all times HAART regimens, HIV RNA viral-load and CD4 was as follows:

Table 2 Shows the T-helper CD4 counts and HIV RNA viral load of the patient

T- Helper CD4 counts	HIV RNA Viral Load	Date
268	1749	Baseline
240	88	2008
249	1029	2009
319	10753	2010
294	15742	2011
246	54745	2013
217	54745	2017
236	11128	2018

3.0 Discussion:

Two therapy-related factors that hindered adherence to ART identified by the patient were side effects and complexity of therapeutic regimens (eg, pill burden and dosing frequency). ART is associated with a number of adverse events (AEs) that may negatively impact adherence to therapy. Of those ART-related AEs that contribute to poor adherence, gastrointestinal AEs may, ultimately, be the most consequential. According to a recently published study in which 1096 patients with HIV were retrospectively followed up to determine those factors most likely to cause discontinuation of treatment (which may be regarded as a form of total treatment nonadherence), gastrointestinal AEs were the primary culprit, accounting for nearly 29% of all discontinuations due to AEs.[7] For this patient, she could not tolerate Kaletra (lopinavir/ritonavir) as it caused her to have diarrhea. Lopinavir/ritonavir-containing antiretroviral regimens are drugs belong to protease inhibitors PIs, and generally well tolerated.[8] PIs are associated with gastrointestinal (GI) disorders. Gastrointestinal disorders most commonly associated with PI usage include nausea, vomiting, abdominal pain, and diarrhea. While all PIs are associated with diarrhea, differing rates of diarrhea have been reported for individual drugs within this class. Although diarrhea can be associated with treatment regimens including PIs, diarrhea can also be related to HIV infection itself.[9] Chronic diarrhea in HIV-infected patients is multifactorial and complex. It can result from opportunistic infections, changes in the intestinal microbial

flora, ARV regimen treatment, viral GI infections, food-borne illnesses, or a combination of these factors. Diarrhea is also associated with ARV regimens other than PIs. This was demonstrated during monotherapy with the NRTI lamivudine (3TC) in which diarrhea was the most common AE.[9.10] Thus, there is potential for additive effects of combination therapies since more than 1 ARV regimen of a combination regimen may contribute to diarrhea. Gastrointestinal AEs are a leading reason that patients switch ART.[9] Therefore; the causing of diarrhea in this patient maybe is not due to kaletra itself as patient thought, but probably due to another reason related to another co-administered drugs. Treatment of diarrhea systematically by giving anti-diarrhea medications including bismuth and loperamide should be considered rather than discontinuation in a patient taking Kaletra.[11] Hence, it is preferred if this patient was given loperamide to treat his diarrhea rather than switching to another HAART regimen , and this could help patient to be more compliance to his medications.

Moreover, latest HAART regimen was given to this patient includes Tenvir Em/Atazanvir/Ritonavir. Patient claimed that the number of pills given are much and cannot take the three medications at the same time as it leads her to have vomiting. As with many diseases requiring complex treatment regimens, adherence to therapy in HIV is strongly affected by how difficult it is to follow the prescribed treatment.[12] Pill burden, which is the number of pills a patient needs to take in a given period, is one important factor in the relationship between dosing and adherence in HIV, and the medical literature shows significantly greater rates of adherence when the pill burden is low.[12] Dosing frequency can also play a significant role in treatment adherence for HIV, as evidenced by the NOCTE study, a 48-week randomized controlled trial in which 87 patients received the same HAART either in a once-nightly or twice-daily dosing schedule. Persistence—which, along with proper execution of a prescribed regimen, is one of the 2 components of adherence—was the main driver of adherence in the study, with 81% of those dosing once nightly persisting with treatment for the full 48 weeks compared with 62% of those dosing twice daily. At the end of the trial period, patients in the once-nightly dosing group were significantly more likely to have been adherent compared with patients in the twice-daily dosing group (P = .03).[13] Thus, fixed-dose ART combinations (FDCs), which combine 2 or more drugs in a single formulation, have been developed to increase the likelihood of treatment adherence.

Several strategies have demonstrated positive effects on treatment adherence in patients with HIV both in terms of managing the disease and in terms of directly addressing barriers to adherence including multidisciplinary care and educational and medication management initiatives.[7]

4.0 Conclusion:

Poor adherence to treatment in HIV is extremely complex both in its myriad causes and in its capacity to negatively affect patient outcomes, treatment options, and healthcare costs. Although the potential negative effects of poor adherence are known, in patients with HIV, adherence takes on particular importance as adherence may impact not only viral suppression, but also the emergence of permanent treatment resistance. Treatment-related factors, patient-related factors, provider-related factors, and healthcare system–related factors may all impact adherences. Consequently, it is important that all participants involved in the management of HIV infection from patients to clinicians to third-party payers recognize and address factors that may potentially reduce treatment adherence.

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