

Medication adherence in schizophrenia

Francisco Javier Acosta, José Luis Hernández, José Pereira, Judit Herrera, Carlos J Rodríguez

Francisco Javier Acosta, José Luis Hernández, José Pereira, Service of Mental Health, General Health Care Programs Direction, Canary Health Service, Las Palmas de Gran Canaria 35004, Spain

Judit Herrera, Carlos J Rodríguez, Insular University Hospital of Gran Canaria, Canary Health Service, Las Palmas de Gran Canaria 35016, Spain

Author contributions: All authors contributed to this paper; Acosta FJ coordinated and led the project.

Correspondence to: Francisco Javier Acosta, MD, PhD, Psychiatrist, Service of Mental Health, General Health Care Programs Direction, Canary Health Service, Consejería de Sanidad 3ª planta, Dirección General de Programas Asistenciales, C/ Pérez del Toro (Plaza Dr. Juan Bosch Millares, 1), Las Palmas de Gran Canaria 35004, Spain. facart@gobiernodecanarias.org

Telephone: +34-928-302764 Fax: +34-928-302797

Received: October 24, 2011 Revised: July 12, 2012

Accepted: September 18, 2012

Published online: October 22, 2012

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Key words: Adherence; Non-adherence; Compliance; Noncompliance; Schizophrenia

Peer reviewers: Vasco Videira Dias, Professor, Department of Psychiatry, Hospital of Santa Maria, Lisbon, Rua Ilha dos Amores, Lt. 4.12C, 1. Esq °, 1990-122 Lisbon, Portugal; Susana Ochoa, PhD, Park St John of God Health, Sant Boi de Llobregat 08330, Spain

Acosta FJ, Hernández JL, Pereira J, Herrera J, Rodríguez CJ. Medication adherence in schizophrenia. *World J Psychiatr* 2012; 2(5): 74-82 Available from: URL: <http://www.wjgnet.com/2220-3206/full/v2/i5/74.htm> DOI: <http://dx.doi.org/10.5498/wjp.v2.i5.74>

Abstract

Non-adherence is a major problem in the treatment of schizophrenia. Its high prevalence, potentially severe consequences and associated costs make the study of this phenomenon a priority issue. In this article, basic non-adherence concepts of prevalence, consequences, evaluation methods, methodological restrictions of available studies, risk factors and intervention strategies, are reviewed. Studying non-adherence risk factors is a necessary step toward designing adequately oriented intervention strategies. An operative definition of adherence and good knowledge of its evaluation methods are essential to study this phenomenon. Unfortunately, most available studies contain methodological restrictions, especially concerning the evaluation methods, and an agreed operative definition of adherence has only very recently been reached. Knowing non-adherence risk factors, intervention strategies and available evidence on their effectiveness is essential in making treatment decisions in daily clinical practice.

INTRODUCTION

In spite of recent progress in the treatment of schizophrenia during the last decades, non-adherence continues to be a frequent phenomenon, often associated to potentially severe clinical consequences^[1,2] and high costs^[3-5]. Estimated non-adherence rates in schizophrenia are about 50%^[6]. These findings together with the fact that non-adherence is considered to be preventable^[2], make the study of this phenomenon a priority objective in psychiatry that includes both the associated risk factors and the efficacy of interventions aimed at reducing it.

Compliance is defined as “the extent to which the patient’s behavior (in terms of taking medications, following diets, or executing other lifestyle changes) coincides with medical recommendations”^[7]. Adherence is defined as “the extent to which the patient’s behavior (in terms of taking medications, following diets, or executing other lifestyle changes) matches medical recommendations jointly agreed between patient and prescriber”^[8,9]. The difference between both concepts is minimal and essentially concerns the physician’s degree of authority^[10].

PREVALENCE

Estimated non-adherence rates in schizophrenia are about 50%, widely ranging from 4% (observed in a study with depot neuroleptic drugs) to 72%^[6]. Factors that might account for such variability include: definition of non-adherence and criteria used to determine it, methods for evaluating non-adherence and observation period^[6]. Furthermore, adherence may vary during the patient's evolution; it is usually good after hospital discharge and tends to decrease with time^[1].

In a prospective study, one-third of patients admitted to hospital after their first psychotic episode of schizophrenia were non-adherents 6 mo afterwards^[11]. Another prospective 2-year study showed similar results: 33.4% of patients stopped attending follow-up visits or refused to go on with the treatment^[12]. In a study including male patients with a first psychotic episode of schizophrenia, schizophreniform disorder or schizoaffective disorder, 53.6% of them abandoned the treatment during the first year^[13].

CONSEQUENCES OF NON-ADHERENCE

In patients with psychopathological symptoms, antipsychotic drugs have proven effective in reducing relapse and rehospitalization rates^[2]; however, non-adherence is a frequent cause of impairment^[6,14], hospitalization^[5,15,16], higher risk of suicide^[17], longer time to remission^[18], poorer prognosis^[19], loss of job, dangerous behavior^[20], arrest, violence, drug and alcohol consumption, psychiatric emergencies, poor mental performance and low satisfaction with life^[21].

The risk of psychotic relapse in patients with schizophrenia and schizoaffective disorder increases almost five times after 5 years, reaching 81.9%^[12]. Furthermore, relapse episodes entail more care related costs^[3-5]. The annual costs of schizophrenia amount to £400 millions in the United Kingdom and over \$10 billion in the United States^[22]; 40% of the costs associated to treatment of schizophrenic persons are attributed to non-adherence^[23].

EVALUATING NON-ADHERENCE

Classification of evaluation methods

Evaluation methods are considered to be "direct" when they offer proof that the patient has taken their medication, i.e., detection of the drug or its metabolites in the organism (generally in serum or urine), detection of a biological marker associated with the drug (or with the placebo) and direct observation of the patient. "Indirect" methods include patient's reports (which may be evaluated through direct questioning or through psychometric scales), tablet count, pharmacy records and the use of electronic monitoring^[24].

From a different point of view, evaluation methods may be classified into "objective" e.g, tablet count, pharmacy records, electronic monitoring devices and drug detec-

Table 1 Adherence evaluation methods

| Direct | Indirect |
|---|---------------------------|
| Detection of the drug or drug metabolites | Objective |
| Direct observation | Tablet count |
| | Electronic monitoring |
| | Pharmacy records |
| | Subjective |
| | Psychometric scales |
| | Questioning the patient |
| | Questioning the relatives |
| | Clinical judgment |

tion in the organism; or "subjective", e.g, patient's reports during interviews or scores rated by an interviewer^[25].

All the available methods have advantages and disadvantages. Detection and determinations of drug levels in serum or urine demonstrate whether the patient has taken the medication but are restricted to recent intake and influenced by inter-subject pharmacokinetic variations^[24]; furthermore, with novel antidepressant and anti-psychotic drugs, such tests are not adequate to determine the amount of drug the patient has taken^[25]. Direct observation is difficult in the case of outpatients. Interviews can be easily conducted but their results depend on the skill of the interviewer, the way of questioning and the reliability of the patient. Tablet count is easy and cost-free but offers no information on the adherence pattern; furthermore the amount of remaining tablets can be intentionally altered by the patient. Useful pharmacy records (new periodic dispensations) need to be complete and include all prescriptions and all pharmacies the patient might access^[24]. Table 1 shows the main evaluation methods.

Subjective impression of the psychiatrist and reports by patients or relatives

Subjective impression of non-adherence has proven unreliable in a number of recent studies, which evidenced adherence overestimation by psychiatrists^[26-30], patients^[27,29,30] and relatives^[29,30]. Studies generally show high sensitivity for detection of adherent patients but poor ability to identify non-adherents^[26,30,31].

Psychometric scales

A number of psychometric scales were developed, aimed at assessing non-adherence by psychotic or specifically by schizophrenic patients. Some of them were validated for other populations of psychiatric patients or for patients with somatic disorders. Some scales were designed to evaluate non-adherence itself; others were focused on related aspects such as the attitude toward medication. Both scale types are complementary^[25].

Available evaluation scales are used to assess different areas. Thus, the Drug Attitude Inventory (DAI)^[32] is used to evaluate the patient's attitude toward medication; the Brief Evaluation of Medication Influences and Beliefs (BEMIB)^[33] and the Rating of Medication

Influences (ROMI)^[34] are based on the model of health-related beliefs; the Medication Adherence Rating Scale (MARS)^[35] is used to evaluate adherence-related attitudes and behaviors; finally, other scales such as the Morisky Adherence Scale^[36] and the Brief Adherence Rating Scale (BARS)^[37] evaluate adherence itself. The later one is the only scale whose validity was demonstrated by comparing it with the results of the Medication Event Monitoring System (MEMS) device^[37]. All of these measures have demonstrated good reliability. However, only the ROMI, BEMIB and BARS scales have shown validity, whereas the information is incomplete or inconsistent for the DAI and MARS scales^[25]. Since all adherence measures have strengths and weaknesses, selection and justification of assessment method should depend on several factors, such as type of adherence area to be evaluated (attitude *vs* adherence itself), type of adherence of interest (pattern of use *vs* discontinuation), time availability, or setting (clinical practice *vs* research study). Whenever possible, those scales with better psychometric properties should be the first choice. Regarding adherence itself, the BARS scale is arguably the first choice, for the reason explained above.

Electronic monitoring; the MEMS device

The MEMS (MEMS: Apex Corp., Fremont, CA, United States) is a medication bottle cap with a microprocessor that records the occurrence and time of each bottle opening, thus allowing for subsequent computer analysis. It is considered the “reference standard” for evaluating adherence^[23,24]. This is the most accurate and efficient method of detecting non-adherence^[24] based on recording periods without signal input^[26]. However, the device is expensive^[24] and has a potential for adherence over-estimation^[26,38] since the occurrence of a bottle opening event does not necessarily correspond with the patient actually taking the medication or the correct dose^[28].

METHODOLOGICAL DIFFICULTIES AND RESTRICTIONS

Definition of non-adherence

Non-adherence is a complex phenomenon, with a wide variety of patterns. From the prescribed medication, the patient might either take lower or higher doses, follow a schedule other than prescribed, completely abandon the treatment^[1] or refuse attending regular visits or being admitted to hospital^[22]. Furthermore, the pattern may change in different phases of the disease^[39,40].

A major problem emerging in related literature published until recent years involves disagreement in the definition of non-adherence and the criteria for considering it clinically relevant^[29,41]. Fortunately, an international consensus document was recently published on adherence to treatment by patients with serious and persistent mental disorders^[42-44]. Current criteria for defining non-adherence are: less than 80% of prescribed medication taken or gaps in medication of at least 7 d^[42].

Evaluation method

A major difficulty and restriction of available studies on adherence is the lack of validated evaluation methods^[23,26]. Most studies are based on indirect and subjective measurements such as information reported by patients or their relatives, or review of patients’ clinical records^[23,29]. Only in a few studies the reference standard method was used, namely electronic monitoring with the MEMS device^[30]. Additionally, many studies contain methodological deficiencies such as lack of a control group, poor description of the studied sample or unreliable criteria for establishing a definition of adherence^[45].

RISK FACTORS

Identifying the risk factors for non-adherence is a first step toward designing intervention strategies aimed at reducing this phenomenon^[6]. The cause of non-adherence is multifactorial^[1].

Non-adherence risk factors identified up to date include: previous non-adherence^[6,46], poor insight, negative attitude or negative response to treatment, current or past drug-dependency, poor relationship with the therapist, shorter length of illness, hospital discharge without an adequate follow-up plan or environment^[6], distress associated with specific side effects or general fear of side effects, inadequate efficacy with persistent symptoms and believing that medication is no longer needed^[42]. Risk factors have traditionally been classified into: patient-related, environment-related, physician-related and treatment-related risk factors^[47,48].

Patient-related risk factors

Sociodemographic factors: Non-adherence was reported to be more frequent in men than in women^[42,48], though not in all of the relevant studies^[6].

Regarding patient’s age, younger patients show higher non-adherence rates than older ones^[31]. At the beginning of the disease, patients may distrust the diagnosis and the need for treatment, and show poorer tolerance to adverse effects^[49]. However, older patients may fail to adhere to treatments because of cognitive deficit, including working-memory loss and impaired executive performance^[50]; furthermore, they are often prescribed multiple treatments. Marital status was not found to be a risk factor. Some studies include financial difficulties^[48,49] and low education level^[38] among the risk factors. Thus, even when every patient should be individually evaluated, a highest-risk profile may be generally defined as corresponding to a male, young patient with low socioeconomic status^[42].

General clinical factors: Although drug and alcohol consumption was suggested to be a major risk factor for non-adherence^[6,46,48,51], such an association was not found in recent studies based on the use of MEMS^[28,30,38]. Association between adherence and length of illness was also not found in the later two studies; however, in other studies an association between higher non-adherence and

longer length of illness was reported^[28]. Previous non-adherence was consistently found to be a risk factor for subsequent non-adherence^[6,42,52].

Psychopathological symptoms: Most studies based on subjective methods^[6], psychiatrist's clinical impression^[53] and a recent expert consensus^[42] indicate that impaired insight is a risk factor for non-adherence. Such an association was also found in studies using the MEMS device^[30,54], although not in all of them^[28,38]. Insight in schizophrenia is a complex and multidimensional phenomenon. Several studies have showed an association between insight and attitudes toward medication^[55-57]. Besides, an association between this latter and adherence to pharmacological treatment has been found in prospective^[58,59] and cross-sectional studies^[41,60-62]. More specifically, implicit, but not explicit, positive attitudes predicted increased insight and perceived need for treatment^[62]. Implicit attitudes are automatically activated evaluative impulses that are difficult to control and potentially outside conscious awareness^[62].

Regarding psychotic symptoms, the content of delusions may influence non-adherence. Patients with delusions of persecution or poisoning are more reluctant to take medication and those with delusion of grandeur are hardly convinced that they need it^[48]. In a prospective study with a 2-year follow-up period on patients with psychotic disorders in their first hospitalization, higher baseline intensity of delusion and suspiciousness were associated with non-adherence during subsequent follow-up^[63]. Persistent psychotic symptoms may promote non-adherence^[42].

Findings relating negative symptoms are controversial. These symptoms have been reported to be predictive of both adherence and non-adherence^[48]. Severe negative symptoms were assumed to impair adherence through their impairing effects on patient's basic self-care abilities^[49]. Negative symptoms may interfere with the will or the ability to take medication, thus impairing adherence^[42]. Other authors claim that available data are scarce and inconclusive^[42].

The role of neurocognitive impairment in non-adherence is a complex and scarcely studied issue^[6]. Some authors reported it to be associated with non-adherence^[39,64,65]. Cognitive impairment in schizophrenia includes deficiencies in attention and memory^[66], two processes necessary for continuing adherence^[67,68]. Neurocognitive impairment is likely to negatively influence adherence by causing oversight, comprehension difficulties or deficient organization regarding medication schedules.

Furthermore, it was suggested that illness severity is not necessarily a cause of non-compliance, but it may act in a bidirectional fashion, i.e., non-compliance causing worsening of symptoms and worsening leading to lower compliance^[69].

Psychological factors: attitudes, beliefs and other subjective aspects: The attitudes and beliefs related with

health, disease and treatments are consistently associated with adherence^[45]. Attitudes vary widely, from very positive to very negative ones, and may change during the course of the disease. Patients who believe that schizophrenia is a mild disorder are more prone to non-adherence^[48]. Positive attitudes toward the treatment have been related with better adherence^[70], while negative ones have been related with non-adherence^[6,31,71]. Other identified risk factors are: negative subjective response to medication^[6], shame of taking medication^[40], stigmatization^[72], believing that the treatment is not needed and that only a minor benefit is derived from it^[73]. Subjective wellbeing is associated with better adherence^[74].

Are there subtypes of non-adherent patients in schizophrenia? Some authors proposed a classification of non-adherent patients into two groups: intentional non-adherents including those who reject medication, and unintentional non-adherents including those with neurocognitive deficiency. Intentional non-adherence would be related with impaired insight, while unintentional non-adherence would derive from cognitive impairment^[30,40] that results in forgetting about the medication or in deficient executive performance^[39]. In case further evidence continues to support such a classification, then different approaches should be developed for the different subgroups. Thus, therapeutic approach to intentional non-adherent patients should focus on improving insight, while approach to unintentional non-adherents should focus on improving cognitive deficiency^[30]. Other authors proposed that patients who reject medication should be distinguished from those who show irregular adherence^[29].

Environment-related risk factors

Environments of poor familial and social support have been associated with non-adherence, both by patients with schizophrenia^[6] and patients with a first psychotic episode^[71,75]. Living alone is a further risk factor^[3,22]. While living with other people usually has protective effects, it maybe a risk factor if the involved interpersonal relationships are perceived as distressing^[48]. In this context, the fact of taking medication may become a distressing element, especially for patients who are not aware of their disease^[2]. Difficulties accessing health services are also a risk factor^[22].

Physician-related risk factors

Having a poor relationship with the therapist^[6], experiencing constraint during hospitalization^[56] and inadequate planning of the post-discharge period were reported to be risk factors for non-adherence^[6]; whereas, a good relationship with the therapist and perceived efficacy of treatment were the main factors associated with adherence^[76]. Both the interest shown by the physician and the psychoeducation and information provided to patients and relatives concerning the disease are important. It is recommended that the attitude toward medication of all medical team members should be consistent^[48].

Treatment-related risk factors

Ineffectiveness of the medication against psychotic or negative symptoms may be a risk factor for non-adherence^[42]. Moreover, antipsychotic drugs exhibit delayed onset of the therapeutic effects (more delayed than adverse effects), post-withdrawal relapse events are not immediate but occur weeks or months later, and many patients in remission fail to perceive a relationship between their improved status and the effects of medication^[48].

Adverse effects have been associated with higher non-adherence rates^[42]. The occurrence of past or present adverse effects of treatment was associated with less favorable attitudes toward antipsychotic treatments and with poorer adherence^[77]. In a prospective study including outpatients with schizophrenia, the main reported reason for non-adherence was fear of adverse effects^[78]. Clinicians should regularly evaluate possible occurrence of such effects and their relevance, when making therapy decisions^[48].

Complexity of the medication schedule might also be a risk factor^[6,20,48]. An association between this variable and non-adherence was found in some recent MEMS studies^[28,79] but not in others^[28,30,38].

Although some studies reported higher adherence with atypical antipsychotic drugs than with classical ones, such a result was not homogeneously observed in these studies^[6,23,70]. Furthermore, reported differences are rather small^[42] and certain side effects of atypical antipsychotics may also impair adherence, such as their metabolic or weight gain effects^[42].

The administration *via* is potentially an important factor. Surprisingly, few studies evaluated adherence to depot or long-acting injected treatments^[6,23,80]; most of them reported high adherence rates for patients with long-term intramuscular treatment, either depot^[2,20], long-acting injection^[80] or both^[30] as compared to oral treatment, as well as lower relapse and re-hospitalization rates^[20,81]. Table 2 shows major risk factors that have been consistently associated with non-adherence in schizophrenia.

ADHERENCE PROMOTING STRATEGIES

Up to date, short-term treatments based on simple interventions have proven efficient, although results are not consistent across different studies. However, long-term treatments require complex interventions, which have not generally proven efficient^[82].

In a recent expert consensus document on non-adherence by patients with serious or persistent mental illness^[42-44] it was recommended that social and pharmacological interventions should be the first line of action^[43]. Combined strategies are recommended^[83], focused on specific adherence-related problems^[42,44] and maintained in the long term^[84].

Patient-related interventions

There is no universal intervention that is adequate for all non-adherent patients; thus, identifying the cause of non-adherence in every particular patient is the first step

Table 2 Identified risk factors for non-adherence by patients with schizophrenia

| |
|---|
| Patient-related risk factors |
| Sociodemographic factors |
| Younger and older patients |
| Male |
| General clinical factors |
| Drugs or alcohol consumption |
| Previous non-adherence |
| Psychopathological symptoms |
| Impaired insight |
| Cognitive deficiency |
| Delusion of persecution, poisoning or grandeur |
| Psychotic symptoms |
| Negative symptoms |
| Psychological factors: attitudes, beliefs and other subjective aspects |
| Negative attitude toward the treatment |
| Negative subjective response to treatment |
| Regarding the disease as mild and/or perceived minor benefit from treatment |
| Shame or stigmatization associated with the medication or the disease |
| Environment-related risk factors |
| Poor social and familial support |
| Negative social perception of the disease |
| Stigmatization |
| Difficulty accessing healthcare services |
| Physician-related risk factors |
| Poor relationship with the therapist |
| Poor psychoeducation and information to patients and relatives |
| Poor contact with the therapist |
| Inadequate planning of the post-discharge period |
| Treatment-related risk factors |
| Ineffectiveness against persistent symptoms (psychotic and negative symptoms) |
| Fear of adverse effects |
| Complex medication schedule |
| Poorer adherence to oral than to intramuscular treatments |

toward establishing a suitable intervention strategy aimed at reducing it^[85].

Thus, interventions are indicated such as: improving insight in patients with poor or no awareness of their disease^[29,30], reducing negative attitudes toward medication^[22,86], reducing psychotic symptoms^[22], reducing drug consumption^[42] and improving cognitive functions^[29,30,68].

Psychosocial interventions

Current evidence suggests that psychosocial interventions are not effective in improving adherence, when applied only to patients^[23] or when attitudinal and behavioral aspects are disregarded^[87]. Family-related interventions have proven efficient, especially long-term ones as well as those combining different strategies^[23,83]. Unfortunately, studies on the maintenance of their efficacy in the long term are very scarce^[88]. In a 2-year prospective study, psychoeducative interventions involving patients and relatives were associated with higher adherence than control, which was maintained all through the 2 years^[89]. However, in patients with a first psychotic episode, family support was a predictor of good medication adherence only for a short period of time, since these patients required persis-

tent family support to stay on medication^[71,75]. This complex and intensive interventions with an approach based on support and problem solving (e.g., assertive community treatment) appear to improve adherence. However, the required resources often restrict applicability of such interventions^[23].

Physician-related interventions

The first step toward improving adherence consists in promoting physicians' awareness that non-adherence is a problem affecting most patients^[2]. Basic recommendations include establishing a good relationship between patient and therapist, dedicating some interview time to evaluate adherence, assessing possible risk factors for non-adherence and making attempts to modify them, evaluating patient's motivation to take medication and trying to improve it if necessary, and involving relatives whenever possible^[90].

Further recommendations^[85] include: performing routine evaluations of adherence, adapting to the patient's needs and allowing the patient to participate in decisions concerning their treatment, promoting effective communication by using the necessary means for the patient to understand the relevant information, accepting that the patient has the right not to take medication (provided that the patient is not disabled and is sufficiently informed), periodically evaluating patient's beliefs and concerns regarding the treatment and offering the necessary information about the disorder and possible therapies.

Pharmacological treatment-related interventions

Atypical antipsychotic drugs were expected to improve adherence, because of their better adverse-effect profiles. However, no consistent findings up to date support better adherence with atypical than with classical oral antipsychotics^[23], although methodological restrictions have been found in those studies^[45]. Recent studies based on the use of MEMS showed no differences between atypical and classical antipsychotics in terms of adherence by patients during the post-discharge period^[79] or outpatients during regular follow-up^[38]. Therefore, clinicians are recommended not to consider good tolerance as equivalent to good adherence.

When possible, pharmacological monotherapy is recommended over polytherapy because of simplicity, less adverse effects, lower risk of drug interactions and easier response evaluation^[20]. Although this issue has been scarcely studied, using treatment schedules as simple as possible is recommended, since possible cognitive deficiencies of patients with schizophrenia could impair memorization and correct execution of complex schedules^[20].

It is important to explain to the patient what they can and what they cannot achieve with the medication. Unrealistic expectancies may lead the patient to abandon the medication when such expectancies are not fulfilled^[2]. Patients should understand and agree with the specific objectives and the therapeutic strategies used to achieve

them. Instructions on medications and schedules should be as simple as possible^[2].

A number of advantages have been reported for depot and long-acting injection treatments, such as: resulting in better adherence, providing the clinician with reliable adherence information^[2], facilitating regular contact between the patient and the therapeutic team^[91], being easier to remember than daily oral treatments^[20], providing immediate detection of non-adherence thus facilitating early intervention^[48], preventing antipsychotic drug substitutions due to assumed inefficiency from relapse episodes that are actually caused by non-adherence^[20], allowing the physician to conduct interviews without questioning on medication to those patients that perceive such questioning as surveillance^[20], and preventing the first-pass-through-liver phenomenon^[91]. Despite their advantages, such treatments are not currently used to their highest potential^[2,92]. There is the generalized belief that patients will be reluctant to them. However, if the physician takes time enough to explain these treatments to the patients, showing conviction on their effectiveness, most patients will agree to start with them^[2]. Authors have reported very high adherence rates, up to 96%, in patients under depot treatment^[93], 85% with long-acting injected risperidone^[80] and 97% with long-acting injection and depot^[30].

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