Background

Morbidity and mortality among people infected with the human immunodeficiency virus (HIV) has declined dramatically since 1996 with the advent of a powerful antiretroviral therapy (ART) and the use of appropriate prophylaxis against opportunistic infections [1, 2]. Formerly considered a terminal illness, HIV infection is now categorized as a chronic disease. Though they cannot eradicate HIV, existing viral therapies suppress its replication and thus make it possible to maintain and improve the immune function of infected persons. However, therapy interruption, even if just temporary, allows the virus to multiply and then develop a resistance to medication [3-6]. This is why it is imperative for therapy adherence to be optimal [7]. Resistance reduces treatment response and allows the disease to progress. This resistance can be transmitted, thus becoming a public health issue. Developing interventions to boost and sustain antiretroviral therapy (ART) adherence has become a critical objective in the field of HIV and its treatment.

Interventions to foster adherence

Treatment adherence immediately arose as a key issue upon the introduction of ART on account of the complexity of the regimen. The need to develop appropriate support interventions to foster adherence was blatant. Since then, the results of pilot studies demonstrated the feasibility of interventions to influence adherence [8-10] and some interventions evaluated by means of experimental studies demonstrated a capacity to optimize this adherence [11-18]. However, systematic reviews of treatment adherence interventions intended for persons living with HIV [19, 20] or other clienteles [21-23] have all concurred that no one intervention was better than any other. What's more, in their recent review, Haynes et al. [21] indicated that only 36 of the 83 interventions that they examined were associated with improved adherence. Kripalani *et al.* [24]

reported similar results in their review of interventions intended to optimize medication adherence in a clientele with a chronic health condition. Of the 37 randomized trials that they looked at, 20 produced a significant change in at least one adherence marker and just over half of these interventions (n=11) had an impact on clinical markers.

In the light of these mixed results, Haynes et al. [21] stressed the need for novel approaches to support treatment adherence. In this regard, tailored interventions and the use of information technologies open up interesting possibilities for developing innovative interventions geared to optimizing treatment adherence and reaching a broader clientele across vast geographical areas.

Information and communications technologies: a promising avenue for providing support to PLHIV

In the field of health education, there is a growing and apparently inevitable tendency to use information and communications technologies (ICT), such as web applications and software systems, as interactive means of information transmission [25-28]. These technologies make it possible not only to present a large amount of data in a more user-friendly mode but also to access, at one's convenience, information better adapted to one's own needs. This particularity greatly facilitates the active learning process at the heart of the development and reinforcement of health behaviour self-management skills [29-31].

Tailored interventions are defined as change strategies intended for a given person based on his or her specific characteristics identified beforehand through an individual evaluation [32, 33]. What distinguishes these interventions is the fact that the change strategy targets the needs of one

particular person rather than those of a group and that the messages and feedback conveyed are adapted to individual factors related to a given health behaviour [34]. This makes it possible to achieve more significant results as the person feels more concerned by the messages and engages more readily in the proposed strategies [35-37].

The combined benefits of tailored interventions and of the use of ICT are what make this type of intervention more effective than traditional health education interventions [31]. Studies have evidenced the efficacy of this type of intervention on the adoption of various health behaviours, including quitting smoking [38-42], reducing the amount of fat in one's diet [43, 44], increasing the consumption of fruit and vegetables [45, 46], and engaging in early cancer detection [47, 48]. In the field of HIV, ICT have been used to encourage the adoption of safe behaviours whether in terms of sexual practices or sharing dirty syringes [49-53].

In their review of computer-assisted tailored interventions delivered online, Lustria and colleagues [54] identified 30 studies (out of the 503 found between 1996 and 2007) where the applications targeted primarily four health behaviours: nutrition (n=10), physical activity (n=7), tobacco use (n=7), alcohol consumption (n=3), and other behaviour (n=3). In their analysis, they sought in particular to describe the mechanisms used to operationalize the concept of tailored interventions and to implement online interventions. They found a wide variety of approaches and highlighted the importance of pursuing research in this domain.

The systematic review by Murray, Burns, See Thai, and Nazareth [55] supported the effects of computer-assisted interventions among persons living with a chronic condition (n=24) in terms

of knowledge acquisition, changes to health behaviour, self-efficacy, perceived social support, and other clinical markers. These technologies have been used with clienteles living with asthma [56], diabetes [57-59], heart disease [60-63], and HIV [64, 65]. On the whole, what emerges is that these technologies can be used with a variety of clienteles of different ages [66-70]. The use of different ICTs in the field of health education shows that they are effective in transferring knowledge and developing the skills needed for health promotion and management of the demands inherent to illness [26, 27].

Regarding access to these technologies, 175 million adults [71] in the United States reportedly used the Internet to obtain health-related information. According to the results of a Harris Poll, 88% of adults online have searched the web for such information. Moreover, in 2009, Statistics Canada [72] reported that 80% of Canadians 16 years of age or over used the Internet at home for personal reasons. This percentage amounted to 21.7 million users. These Canadian data revealed also that 70% of people used the Internet to search for medical information and for health-related purposes (74% of women and 66% of men). In Quebec, the second most densely populated province in Canada, the *NETendances* survey conducted by CEFRIO-Léger Marketing [73] revealed that 79.1% of Quebecers had used the internet in the seven days prior to responding to the survey.

To date, web applications have been developed to support primary and secondary prevention efforts, including with respect to tobacco use, physical activity, nutrition, the use of certain health exams, and the adoption of safe sexual behaviours. However, few tailored interventions have used this educational approach in tertiary prevention to support therapy adherence. Living

with HIV makes considerable demands on a person in terms of self-management, especially regarding adherence to a complex therapy and coping with adverse side-effects. PLHIV must play a more active role in this management, thus altering the traditional paternalistic health model where the patient has a more passive role. The health professional, instead, becomes a care partner and mentor who empowers the PLHIV to take charge of the situation. Consequently, it is imperative that innovative ways be found to provide assistance and follow-up to PLHIV. From this point of view, we believe that the use of ICTs can constitute an effective approach to therapy management by providing PLHIV with support in the form of messages that target and are adapted to their needs. Such virtual follow-up would be complementary to existing clinical follow-up. Given the persistent or long-term nature of ART, finding new ways to support PLHIV who are under such treatment appears an avenue worth exploring.

Goal

Drawing on the recommendations of the National Institutes of Health [NIH, 74] regarding the four phases of research on interventions in the field of health sciences, we plan to evaluate the efficacy of an online virtual intervention in optimizing adherence to antiretroviral medication intake among PLHIV (phase III). The study will rest on preliminary work – phases I and II – that served to clearly identify the predictors of therapy adherence among PLHIV [75], develop and validate the content of the intervention in question [76], and create the corresponding Web application [77].

Preliminary work

Based on a philosophy of empowerment, the HIV Treatment, Virtual Nursing Assistance and Education (VIH-TAVIE™[i]) Web application makes it possible to develop and strengthen the skills needed to self-manage therapy while boosting one's sense of self-efficacy with respect to the daily intake of medication [77]. This application was developed following the systematic analytic process proposed by Bartholomew, Parcel, Kok, and Gottlieb [78, 79] and rests on explanatory and predictive models of health behaviours [76]. The specificity of this application lies in its action mechanism based on Bandura's theory of behavioural change [80], which targets the development and reinforcement of skills, that is, the individual's ability to act.

More specifically, the Web application is composed of four interactive computer sessions hosted by a virtual nurse who engages the PLHIV in a medication-intake self-management skills-learning process. The skills covered (motivational, self-awareness, problem-solving, emotion-regulation, social) allow the PLHIV to integrate the therapeutic regime in his or her daily routine, to manage adverse side-effects, to handle problem situations that might interfere with medication intake, to interact with health professionals, and to mobilize his or her social support network. Aside from delivering tailored teaching, the virtual nurse refers to the experiences of other persons who coped with similar situations successfully. During these sessions, the virtual nurse provides feedback and positive reinforcement on the PLHIV's personal style and methods and on the acquired skills. The interactive system is designed to allow repeated applications and backtracking depending on the PLHIV's needs. Moreover, at each session, feedback is provided on the significant elements of the previous session. The PLHIV's profile is personalized as a function of his or her needs and characteristics, thus giving the profile a tailored fit. Furthermore, the computer innovation underlying the virtual intervention allows creating new pages of one's

own, thus allowing the system administrator the flexibility to add or modify page models and content depending on the context.

Method

Design

We opted for an online randomized controlled trial to evaluate the efficacy of the virtual intervention (Web application) primarily in influencing ART adherence. Adherence is a behavioural indicator that can be predicted in part by cognitive and affective variables, particularly sense of self-efficacy and attitude towards antiretroviral medication intake [75]. These variables are in turn explained by perceived social support, relationship with health professionals, and absence of adverse effects. These intermediate variables, which are the targets of our intervention, will allow effective change in the short term. They constitute mediators capable of explaining the intervention's effect on adherence. There will be three measurement times: pre-intervention (T0), at 3 months (T3), and at 6 months (T6). Participants will be drawn from a convenience sample and will be randomly assigned either to an experimental group, which will use our Web application, or to a control group, which will be presented with a list of various Web sites of interest.

Hypotheses

Primary hypothesis: A higher proportion of participants in the experimental group will prove treatment-adherent at T6 compared with the control group. Explanatory hypothesis: The following variables are considered mediators that can explain the intervention's effect on

adherence: sense of self-efficacy, attitude towards antiretroviral medication intake, degree of symptom-related discomfort, and perceived social support (T0, T3, T6).

Sample

We aim to constitute a sample of 232 participants, that is, 116 per group. The PLHIV who will participate in the study must be at least 18 years of age and under ART for at least six months. The reason for the latter criterion is that we wish the therapy management intervention to focus on adherence over time rather than on treatment initiation. Internet access is another inclusion criterion. This last criterion will introduce a selection bias in the study. However, the bias will be offset by the inherent value in evaluating an innovative service-delivery modality that, in the near future, could reach a vast clientele at low cost and, thus, constitute a non-negligible option for providing follow-up to clienteles with a chronic health problem. In the end, both the experimental group and the control group will be composed of PLHIV with similar characteristics, who have Internet access and who use it to obtain information relative to their health condition.

The sample size was estimated based on the studies by Tuldrà *et al.* [81] and Pradier *et al*. [16] carried out with PLHIV and on the systematic review by Haynes [21] of adherence-related interventions intended for various clienteles. In the study by Tuldrà *et al*.[81], a difference of 25 percentage points was observed between the control group and the experimental group in terms of treatment adherence (69% vs. 94%, respectively). For Pradier *et al.* [16], the proportion of treatment-adherent participants was 58% in the experimental group and 63% in the control group at the start of the study and 75% and 60%, respectively, following the intervention. We

calculated our sample size on the assumption that the proposed intervention (the Web application) will increase the percentage of treatment-adherent participants in the experimental group by 20%. We will use as percentage of treatment-adherent participants at the start of the study the one reported by Godin *et al*., [75], that is, 50%, our recruitment pool being very similar to theirs. This is a conservative assumption given that the variance in the difference between the two proportions will be larger with the benchmark proportion set at about 50%. Consequently, the sample size required to detect a difference of 20 percentage points (50% treatment-adherent participants in control group vs. 70% in experimental group) will be larger than for other scenarios with the same 20-point difference. Hence, in order to detect a difference of 20 percentage points at 80% power and a χ^2 test two-tailed α value of .05, the required sample size is 186 participants, that is, 93 per group. As we are assuming a 20% attrition rate, that is, the same rate observed in the studies by Goujard *et al*. [12] and Tuldrà *et al.* [81], the sample size is set at 232 participants. With a sample of 186 participants completing the study, the statistical power will be enough to detect a moderate effect on the intermediate variables. In particular, with N=186, a Student's t test two-tailed α value of .05 will allow detecting the difference between the two percentages, corresponding to a standard deviation of 50% and power above 90%.

Experimental condition

The virtual intervention consists of four computer sessions of 20 to 30 minutes. There will be a one-week interval between sessions to ensure the progressive acquisition and consolidation of skills. Thus, access will be controlled and predetermined within this interval. It will be possible at all times by participants to revisit previous sessions. Access will be unlimited in terms of

intensity, frequency, and time of use for the duration of the study. Delivering an intervention by computer affords a key advantage, namely, that of exercising complete control on the content. Moreover, the intervention's parameters are recorded, thus making it possible to obtain a reliable picture of the actual intensity, duration, and frequency of the intervention. These data will be available for subsequent analyses.

Control group

Participants in the control group will be invited to consult, at their convenience and from the location of their choice, a list of predetermined Web sites offering information on antiretroviral medication, their side-effects, and their interactions.

Measurement

Adherence constitutes the principal outcome. For the purposes of the study, it will be evaluated through a self-administered questionnaire that was developed for and validated on the targeted population in accordance with recommendations relative to the measure of therapy adherence [82]. The questionnaire comprises seven items that serve to determine how many times a person forgets to take his or her medication. The questionnaire is designed to place the respondent in a context where events and situations could lead to lapses. The questionnaire's validity was demonstrated (sensitivity: 71 %; specificity: 72%; correct classification: 72%; odds ratio: 6.15) using immunologic (CD4 count) and virologic (viral load) parameters as validation criteria. Adherence is defined as the intake of at least 95% of prescribed tablets.

The intermediary measures will be assessed by means of validated instruments:

Self-efficacy regarding medication intake will be measured using 12 items rated on a 5-point Likert scale. These items are adapted from a scale developed by Godin et al. [75] and previously used on a large sample (*N*=399). To adapt the instrument to our context, that is, antiretroviral medication intake, the items were reformulated by expert consensus following the results of a focus group and of a literature review, and on the basis of Bandura's theoretical model of self-efficacy. A content validation was carried out.

Attitude toward medication intake will be evaluated through six items rated on a 5-point Likert scale. These items emerged from focus groups of PLHIV under treatment. A preliminary version of the instrument was tested on 35 PLHIV. The scale was previously used on a large sample (*N*=399) [75], obtaining a Cronbach's α coefficient of .83 and a test-retest reliability coefficient of .72.

Symptom-related discomfort will be measured with the Self-Completed HIV Symptom Index [83]. This 20-item instrument determines whether symptoms are present on a scale of 0 to 4 (absence 0) and the degree of discomfort experienced (1, 2, 3, or 4). The instrument was validated on 188 PLHIV, demonstrating acceptable psychometric properties, including good construct validity.

Social support will be evaluated using the Medical Outcome Survey [84, 85]. One dimension of social support will be measured by the following subscale: emotional support (8 items). Each item is rated on a 5-point Likert scale. The instrument has demonstrated good content validity and appreciable internal consistency.

A sociodemographic questionnaire will cover personal characteristics such as sex, age, family situation, level of education, employment situation, number of children, and questions regarding HIV, the therapeutic regimen, and presence of symptoms.

Recruitment and online data collection

The study will be conducted entirely online. The project will be advertized on the Web sites of resources available to PLHIV, where a hyperlink and a banner will be inserted to redirect parties interested in participating in the online research. The targeted resources include partner clinics, community agencies, and other organizations that deliver teaching, care, treatment, or follow-up to PLHIV. In addition, health professionals and stakeholders will be invited to inform their clienteles about the study. In order to promote the project among PLHIV, different communication strategies will be used: 1) traditional methods, such as poster and information brochures; and 2) technological or virtual methods, by advertising the study on Web sites of organizations (medical clinics, association for PLHIV) frequently visited by PLHIV.

Persons who will visit the study's Web site will view a short videoclip of testimonials by a few PLHIV. Then, they will be given information on the study. After accepting the conditions of the study and consenting to take part in it, they will sign up for the study by providing an email address and a nickname. Each participant will be validated through an email address check. Once this step completed, a hyperlink will be emailed to allow participants to access the first questionnaire online on our Web site. It is only after having completed this questionnaire that they will be randomly assigned by the computer system to the experimental group or the control group. Participants in the control group will be invited to consult predetermined Web sites that

offer information on ART and their side-effects. Participants in the experimental group will be offered the virtual intervention through the Web application. Three and six months after the initial measurement, participants will complete the online questionnaires again. A reminder to this effect will be emailed to them in the days prior to the measurement. Participants will be compensated for their time spent on the study with an Amazon.ca gift certificate for each measurement time completed.

Type of analysis used

To establish whether the experimental and control groups are equivalent, the means and medians of continuous variables and the frequency distributions of discrete variables will be compared by means of descriptive analyses. The principal analyses will focus on comparing the two groups in terms of treatment adherence, the study's main outcome (considered as a binary variable: adherent ≥ 95% or non-adherent < 95%) at the end of follow-up at T6. An intention-to-treat (ITT) analysis will be carried out to evaluate the true value of the intervention in a real context. Consequently, in the following analyses, all participants will be studied in their respective randomization group on whether they follow the procedure or are lost to attrition during follow-up. In accordance with the principles of ITT, participants who drop out and for whom there will be no adherence measure at T6 will be considered as non-adherent.

The primary hypothesis is that the VIH-TAVIE intervention will increase the proportion of treatment-adherent patients at T6. This hypothesis will be tested using a chi-square test with 1 degree of freedom. If preliminary analyses show that the two groups differ on certain characteristics, multivariate logistic regression will be used to adjust the intervention's effect on

these characteristics considered as potential confounding variables. In this case, a two-tailed Wald's test will be used to test the intervention's adjusted effect.

For the secondary analyses, the two groups will be compared on all the repeated measures of adherence (T3-T6) using a GEE approach that generalizes the logistic regression for longitudinal data with repeated measures of the binary measure [86] We will assume that the covariance matrix has an auto-regressive (AR) structure of order 1 to account for inter-correlations among repeated measures (over the course of follow-up) with the same participants. The difference between repeated measures of adherence (T3 and T6) will constitute the binary dependent variable. The binary intervention indicator, as well as the indicator of time since the follow-ups (3 and 6 months) and, if necessary, the confounding variables will be included as independent variables. Finally, the interaction between the intervention effect and the time effect will be added to the GEE model and will be tested to verify whether the intervention's effect on adherence varies over time. In the GEE analyses, a conservative approach will be used and, accordingly, all missing data for the dependent variable (adherence) will be replaced with "non-adherent". The same approach will be used to evaluate the effects of the intervention on the repeated measures of the intermediary variables. However, given that these variables will be measured by means of quantitative scales, a linear mixed model for repeated measures of a continuous dependent variable [87] will be used instead of the GEE model.

Challenges of online RCT

Carrying out this online randomized controlled trial (RCT) poses various challenges, particularly in terms of recruitment, ethics, and data collection, including participant follow-up over an extended period of time [88].

First, to attract and retain the online participation of PLHIV interested in the study, the team sought the help of Web design experts. This help led to the development of a brand image (concept of *branding*) by an artistic director who created a logo that would carry the image of the study and be easily recognizable by our target group. This *branding* set the tone (in terms of colour, visuals) for our HTML pages, which were created to be visually attractive to participants. More specifically, upon reaching the very first page of the Web site, participants will listen to testimonials by a few PLHIV about their own actual experiences with medication intake and with surfing the Web in search of health-related information. Aside from being an interesting and dynamic visual tool, we used testominals to allow potential participants to identify with the intervention and to humanize and personify the Web-based study. These testimonials also have the potential to strengthen the branding of the intervention. Then, in a short videoclip, the research coordinator and a project spokesperson present information on the study, including its aim and inclusion criteria, and explain what participation entails.

Various communication strategies will be used to promote the study among PLHIV. First, traditional methods of dissemination will be employed, such as publishing ads or short articles in magazines aimed at PLHIV, and distributing information brochures and posters to the clinics and community organizations targeted. Second, an Internet-based approach will be utilized as well, consisting of posting a hyperlink to our study on the Web sites of organizations (medical clinics,

association for PLHIV, community groups) frequently visited by PLHIV. In this regard, Birnbaum [89] suggested that such organizations run ads in their electronic newsletters. A list of targeted Internet media will be compiled in collaboration with key informants working with PLHIV in community organizations. There are other methods of online recruitment, such as reaching target groups through *chatrooms*, sending e-mailings to pre-established lists of participants, or posting banners on popular Web sites [90, 91]. However, these last strategies will not be used in our study. According to Noseck *et al*., [91], even if posting ad banners is a popular way of promoting a study, it remains a costly way of recruitment and "is not the most effective at netting traffic" (p. 167).

One of the risks that remain difficult to control or prevent in a virtual environment is having the same person participate more than once in the study [89, 91, 92]. Although this has been shown to be a rare phenomenon [3%, 89, 93], certain strategies can be put forth to detect (prevent) it and reduce the risk of its occurrence: warning participants to register only once, asking for an email address and a password at registration, filtering data that appears to be identical, and so on [89, 91, 92].

The ethical aspects of online studies have been discussed by various authors [94-97]. The topic has received a special treatment on account of the absence of direct interaction between researchers and participants and the particularity of the online research environment [91, 92]. Among other things, consent can be presented in the form of a statement to be read and checked off before clicking on an "I agree to participate" button. A "Withdraw" or "Leave the study" button [91] will be accessible to allow participants the freedom to drop out of the study at any

time. As proposed by Hewson [95] and Nosek *et al*. [91], a "debrief page" and contact information for a resource person in the event of questions or problems will be provided. The information must be presented in such a way as to properly inform participants but without overwhelming them with data, which could bog things down and turn people off. The study has been approved by the Research Ethics Board of Université de Montréal and the Center of research of the Centre Hospitalier de l'Université de Montréal.

The security and confidentiality of electronic data in online studies are serious concerns that necessitate the implementation of stringent measures. The data collected through the online questionnaires will be stored on a secure server located at the Research Centre where the research work is carried out. Only system administrators will have access to the data on the server. To protect the identity of participants, only an email address and an alias will be requested of participants, this information being necessary to ensure follow-up and disseminate results, as pointed out by Michalak and Szabo [96]. Using a firewall, encrypting the data, protecting passwords, and separating the sociodemographic data from the experimental data (linking them through a code) reduces the risk of an unauthorized third-party accessing confidential content [91, 97]. A database has been planned subsequently to support the direct transfer of the data to SPSS in order to facilitate data analysis.

As underscored by Bull *et al*. [90], online longitudinal evaluations entail following up on participants and completing the various measures. According to Bull *et al.* [90] and Bennett and Glasgow [88], there is a lower retention rate in online studies than in traditional studies. Attrition rates of 40% are not uncommon. However, Schubart *et al.* [98] and Bull *et al*. [99] highlighted a

number of elements that foster a high retention rate in online studies, including the availability of a health professional to provide feedback, the dynamism of the study Web site, and the inclusion of a clinician-coach in the intervention, such as a nurse. These will be considered in this study.

For the purpose of encouraging participants to continue with the study, reminder emails (max. 3-4) will be sent out at 7-day intervals (prior to measurement). In this regard, Bull and colleagues [90] noted that emails were not enough to communicate with participants and that a variety of communication modes should be used. To this end, participants should be asked to provide a home telephone number, a mobile telephone number, a home address, and so on. According to these authors, a balance must be struck between guaranteeing confidentiality and ensuring follow-up. As the technological universe used is complex and can present many problems and bugs, we plan to assign a resource person to help users in this regard (technical support). According to Paul and colleagues [97], this constitutes a key source of support when the research budget allows it.

A research project that unfolds entirely online necessitates that all parties share an understanding of the specific terminology used by the various experts involved and of the role played by the professionals in each of the project's teams (i.e., computer programming, multimedia, clinical). It is necessary to think "virtual", that is, to render procedures applied in the real world operational online. Transposing research procedures to an entirely virtual research intervention entails anticipating the entire sequence of participation and follow-up of the targeted persons. Making this shift is not easy. Indeed, the absence of a common language between research, clinical, and Web media teams, as well as a mutual misunderstanding of the needs of each group (researchers

vs. tech support teams), calls for a great deal of clarification and meetings to make the technical operationalization required by the project possible. This association between researchers deriving from clinical disciplines (nursing, medicine), experts in behavioural and educational sciences, and information technology and media experts is at the root of the creation of absolutely singular teams conducive to the development of innovative solutions to supplying and delivering services to those who need them.

However, without the contribution of community partners and other clinical collaborators, such a study could not be carried out as easily. Their support and expertise are invaluable at different levels, particularly in planning and developing the different stages of the online study (e.g., use of testimonials was their idea). Our partners will also be involved in promoting the study, in recruiting participants, and ultimately in transferring and implementing the virtual intervention.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

The study is funded by the Fonds de la recherche en santé du Québec (FRSQ, 2008-2012). JC has received a clinical research bursary (Junior 2) from the FRSQ (2009-2013) to support her research program on innovative virtual interventions that are intended for persons living with a chronic health problem. The plateform TAVIE received financial support from the Réseau Sidami du FRSQ.

Author details

[1]Research Chair in Innovative Nursing Practices, Research Center of the Centre Hospitalier de l'Université de Montréal, Québec, Canada.[2]Faculty of Nursing, Université de Montréal, Québec, Canada. [3]Canada Research Chair on Behavior and Health, Laval University, Quebec, Canada.[4]Canada Research Chair on Software Patterns and Patterns of Software, École polytechnique, Québec, Montréal. [5] Canada Research Chair in Health Education, Université du Québec à Montréal, Québec, Canada. [6] Quebec coalition of community based HIV/AIDS organisations (COCQ-SIDA), Montréal, Québec, Canada. [7] Faculty of Medicine, Université de Montréal, Québec, Canada.[8]Research Center of the Centre Hospitalier de l'Université de Montréal, Québec, Canada.

Author's contributions

JC and GG drafted the study protocol. JC and GR adapted the protocol for the publication. All authors critically revised and approved the final manuscript.

References

1. Casalino E, Wolff M, Ravaud P, Choquet C, Bruneel F, Regnier B: **Impact of HAART advent on admission patterns and survival in HIV-infected patients admitted to an intensive care unit**. *AIDS* 2004, **18**:1429-1433.
2. Hogg RS, Yip BK, C., Craib KJP, O'Shaughnessy MV, Schechter MT, Montaner JSG: **Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens**. *Can Med Assoc J* 1999, **160**(5):659-665.
3. Descamps D, Flandre P, Calvez V, Peytavin G, Meiffredy V, Collin G, Delaugerre C, Robert-Delmas S, Bazin B, Aboulker JP *et al*: **Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy**. *J Am Med Assoc* 2000, **283**(2):205-211.
4. Harrigan PR, Hogg SR, Dong YW, Yip B, Wynhoven B, Woodward J, Brumme CJ, Brumme ZL, Mo T, Alexander CS *et al*: **Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy.** *J Infect Dis* 2005, **191**:339-347.
5. LeMoing V, Chêne G, Leport C, Lewden C, Duran S, Garré M, Masquelier B, Dupon M, Raffi F, the Antiproteases Cohorte (APROCO) study group: **Impact of discontinuation of initial protease inhibitor therapy on further virological response in a cohort of human immunodeficiency virus-infected patients**. *Clin Infect Dis* 2002, **34**(2):239-247.
6. Lucas MG: **Antiretroviral adherence, drug resistance, viral fitness and HIV disease progression: a tangled weg is woven.** *J Antimicrob Chemother* 2005, **55**:413-416.
7. Paterson D, Swindells S, Mohr J, Brester M, Vergis E, Squier C, Wagener MM, Singh N: **Adherence to protease inhibitor therapy and outcomes in patients with HIV infection**. *Ann Intern Med* 2000, **133**(1):21-30.
8. De Bruin M, Hospers HJ, Van den Borne HW, Kok G, Prins JM: **Theory -and evidence-based intervention to improve adherence to antiretroviral therapy among HIV-infected patients in The Netherlands : a pilot study**. *AIDS Patient Care STDS* 2005, **19**(6):384-393.
9. Dilorio C, Resnicow K, McDonnell M, Soet J, McCarthy F, Yeager K: **Using a motivational interviewing to promote adherence to antiretroviral medications: a pilot study.** *J Assoc Nurses AIDS Care* 2003, **14**(2):52-62.
10. Kalichman SC, Cherry J, Cain D: **Nurse-delivered antiretroviral treatment adherence intervention for people with low literacy skills and living with HIV/AIDS**. *J Assoc Nurses AIDS Care* 2005, **16**(5):3-15.
11. Chiou PY, Kuo BI, Lee MB, Chen YM, Chuang P, Lin PC: **A program of symptom management for improving quality of life and drug adherence**. *J Adv Nurs* 2006, **55**(2):169-179.
12. Goujard C, Bernard N, Sohier N, Peyramond D, Lançon F, Chwalow J, Benoit A, Delfraissy J-F: **Impact of a patient education program on adherence to HIV medication: A randomized clinical trial**. *J Acquir Immune Defic Syndr* 2003, **34**(2):191-194.
13. Holzemer WL, Bakken S, Portillo CJ, Grimes R, Welch J, Wantland D, Mullan JT: **Testing a nurse-tailored HIV medication adherence intervention**. *Nurs Res* 2006, **55**(3):189-197.

14. Javanbakht M, Prosser P, Grimes T, Weinstein M, Farthing C: **Efficacy of an individualized support program with contingent reinforcement among nonadherent HIV-positive patients**. *J Int Assoc Physicians AIDS Care* 2006, **5**(4):143-150.
15. Koenig LJ, Pals SL, Bush T, Stratford D, Ellerbrock TV, Palmore MP: **Randomized controlled trial of an intervention to prevent adherence failure among HIV-infected patients initiating antiretroviral therapy**. *Health Psychol* 2008, **27**(2):159-169.
16. Pradier C, Bentz L, Spire B, Tourette-Turgis C, Morin M, Souville M, Rebillon M, Fuzibet J, Pesce A, Dellamonica P *et al*: **Efficacy on an educational and counseling intervention on adherence to highly active antiretroviral therapy: French prospective controlled study.** *HIV Clin Trials* 2003, **4**(2):121-131.
17. Weber R, Christen L, Christen S, Tschopp S, Hansjoerg Z, Schnedier C, Schmitt J, Opravil M, Günthard HF, Ledergerber B: **Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial**. *Antivir Ther* 2004, **9**(1):85-95.
18. Williams BA, Fennie PK, Bova AC, Burgess DJ, Danvers AK, Dieckhaus DK: **Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial.** *J Acquir Immune Defic Syndr* 2006, **42**(3):314-321.
19. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B: **Effectiveness of Interventions to Improve Patient Compliance: A Meta-Analysis**. *Med Care* 1998, **36**(8):1138-1161.
20. Rueda S, Park-Wyllie LY, Bayoumi AM, Tynan AM, Antoniou TA, Rourke SB, Glazier RH: **Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS.** *Cochrane Database Syst Rev* 2006(3).
21. Haynes RB, Ackloo E, McDonald HP, Yao X: **Interventions for enhancing medication adherence (Review)**. *Cochrane Database Syst Rev* 2008(4).
22. Haynes RB, McDonald H, Garg AX, Montague P: **Interventions for helping patients to follow prescriptions for medications**. *Cochrane Database Syst Rev* 2002(2).
23. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP: **Interventions for enhancing medication adherence (Review)**. *Cochrane Database Syst Rev* 2005, **4**.
24. Kripalani S, Yao X, Haynes RB: **Interventions to enhance medication adherence in chronic medical conditions: a Systematic review**. *Arch Intern Med* 2007, **167**(6):540-549.
25. Dorr D, Bonner LM, Cohen AN, Shoai RS, Perrin R, Chaney E, Young AS: **Informatics systems to promote improved care for chronic illness: a literature review**. *J Am Med Inform Assoc* 2007, **14**:156-163.
26. Lewis D: **Computers in patient education**. *Comput Inform Nurs* 2003, **21**(2):88-96.
27. Nguyen HQ, Carrieri-Kohlman V, Rankin SH, Slaughter R, Stulbarg MS: **Internet-based patient education and support interventions: a review of evaluation studies and directions for futrure research**. *Comput Biol Med* 2004, **34**:95-112.
28. Young AS, Chaney E, Shoai R, Bonner L, Cohen AN, Doebbeling B, Dorr D, Goldstein MK, Kerr E, Nichol P *et al*: **Information technology to support improved care for chronic illness** *J Gen Intern Med* 2007, **22**(Suppl 3):425-430.
29. Bental DS, Cawsey A, Jones R: **Patient information systems that tailor to the individual**. *Patient Educ Couns* 1999, **36**:171-180.
30. Lewis D: **Computer-based approaches to patient education.** *J Am Med Inform Assoc* 1999, **6**(4):272-282.

31. Revere D, Dunbar PJ: **Review of computer-generated outpatient health behavior interventions.** *J Am Med Inform Assoc* 2001, **8**(1):62-79.
32. Kreuter MW, Bull FC, Clark EM, Oswald DL: **Understanding how people process health information: a comparaison of tailored and untailored weight loss materiels**. *Health Psychol* 1999, **18**(5):1-8.
33. Kreuter MW, Farrell D, Olevitch L, Brennan L: *Tailored health messages: Customizing communication with computer technology*. Mahwah, NJ: Lawrence Erlbaum; 1999.
34. Kreuter MW, Skinner CS: **Tailoring, what's in a name?** *Health Educ Res* 2000, **15**:1-4.
35. Dijkstra A: **Working mechanisms of computer-tailored health education: evidence from smoking cessation**. *Health Educ Res* 2005, **20**:527-539.
36. Dijkstra A, De Vries H: **The development of computer-generated tailored interventions**. *Patient Educ Couns* 1999, **36**:193-203.
37. De Vries H, Brug J: **Computed-tailored interventions motivating people to adopt health promoting behaviours: Introduction to a new approach.** *Patient Educ Couns* 1999, **36**:99-105.
38. Lancaster T, Stead LF: **Self-help interventions for smoking cessation.** *Cochrane Database Syst Rev* 2003(3).
39. Velicer WF, Prochaska JO: **An expert system intervention for smoking cessation**. *Patient Educ Couns* 1999, **36**:119-129.
40. Walters ST, Wright JA, Shegog R: **A review of computer and Internet-based interventions for smoking behavior**. *Addict Behav* 2006, **31**:264-277.
41. Strecher VJ: **Computer-tailored smoking cessation materiels: A review and discussion**. *Patient Educ Couns* 1999, **36**:107-117.
42. Strecher VJ, Wang C, Derry H, Wildenhaus K, Johnson C: **Tailored intervention for multiple risk bahaviors**. *Health Educ Res* 2002, **17**(619-626).
43. Brug J, Campbell M, van Assema P: **The application and impact of computer-generated personalized nutrition education: a review of the literature**. *Patient Educ Couns* 1999, **36**:145-156.
44. De Bourdeaudhuij I, Stevens V, Vandelanotte C, Brug J: **Evaluation of an interactive computer-tailored nutrition intervention in a real-life setting**. *Ann Behav Med* 2007, **33**(1):39-48.
45. Baker AH, Wardle J: **Increasing fruits and vegetable intake among adults attending colorectal cancer screening**. *Cancer Epidemiol Biomark Prev* 2002, **11**(2):203-206.
46. Pérez-Rodrigo C, Wind M, Hildonen C, Bjelland M, Aranceta J, Klepp KI, Brug J: **The pro-children intervention: applying the intervention mapping protocol to develop a school-based fruit and vegetable promotion programme**. *Ann Nutr Metab* 2005, **49**:267-277.
47. Jerant A, Kravitz RL, Rooney M, Amerson S, Kreuter M, Franks P: **Effects of a tailored interactive multimedia computer program on determinants of colorectal cancer screening: A randomized controlled pilot study in physician offices**. *Patient Educ Couns* 2007, **66**:67–74.
48. Nooijer J, Lechner L, Candel M, de Vries H: **A randomized controlled study of short-term and long-term effects of tailored information versus general information on intention and behavior related to early detection of cancer**. *Cancer Epidemiol Biomark Prev* 2002, **11**:1489-1491.

49. Gilbert P, Ciccarone D, Gansky SA, Bangsberg. DR, Clanon K, McPhee SJ, Calderon SH, Bogetz A, Gerbert B: **Interactive "video doctor" counseling reduces drug and sexual risk behaviors among HIV-positive patients in diverse outpatient settings**. *PLoS ONE* 2008, **3**(4).
50. Kiene SM, Barta WD: **A brief individualized computer-delivered sexual risk reduction intervention increases HIV/AIDS preventive behavior**. *J Adolesc Health* 2006, **39**:404-410.
51. Lau JTF, Lau M, Cheung A, Tsui HY: **A randomized controlled study to evaluate the efficacy of an internet-based intervention in reducing HIV risk behaviors among men who have sex with men in Hong Kong**. *AIDS Care* 2008, **20**(7):1-9.
52. Marsch LA, Bickel WK: **Efficacy of computer-based HIV/AIDS education for injection drug users**. *Am J Health Behav* 2004, **28**(4):316-326.
53. Gagnon H, Godin G, Alary M, Bruneau J, Otis J: **A randomized trial to evaluate the efficacy of a computer-tailored intervention to promote safer injection practices among drug users**. *AIDS Behav* 2010, **14**(3):538-548.
54. Lustria MLA, Cortese J, Noar SM, Glueckauf RL: **Computer-tailored health interventions delivered over the web: Review and analysis of key components**. *Patient Educ Couns* 2009, **74**:156-173.
55. Murray E, Burns ME, See Thai S, Lai R, Nazareth I: **Interactive health communication applications for people with chronic disease (review)**. *Cochrane Database Syst Rev* 2007(4).
56. Joseph CLM, Peterson E, Havstad S, Johnson CC, Hoerauf S, Stringer S, Gibson-Scipio W, Ownby DR, Elston-Lafata J, Pallonen U *et al*: **A Web-based, tailored asthma management program for urban African-American high school students**. *Am J Respir Crit Care Med* 2007, **175**(9):888 – 895.
57. Hee-Sung K: **Impact of Web-based nurse's education on glycosylated haemoglobin in type 2 diabetic patients**. *J Clin Nurs* 2007, **16**(7):1361-1366.
58. Kim CJ, Kang DH: **Utility of a Web-based intervention for individuals with type 2 diabetes: the impact on physical activity levels and glycemic control**. *Comput Inform Nurs* 2006, **24**(6):337-345.
59. Wangberg SC: **An internet-based diabetes self-care intervention tailored to self-efficacy**. *Health Educ Res* 2008, **23**:170-179.
60. Beranova E, Sykes C: **A systematic review of computer-based softwares for educating patients with coronary heart disease**. *Patient Educ Couns* 2007, **66**(1):21-28.
61. Evangelista LS, Stromberg A, Westlake C, Ter-Galstanyan A, Anderson N, Dracup K: **Developing a Web-based education and counseling program for heart failure patients**. *Prog Cardiovasc Nurs* 2006, **21**(4):196-201.
62. Strömberg A, Dahlström U, Fridlund B: **Computer-based education for patients with chronic heart failure. A randomised controlled multicentre trial of the effects on knowledge, compliance and quality of life**. *Patient Educ Couns* 2006, **64**:128-135.
63. Westlake C, L.S. E, Strömberg A, Ter-Galstanyan A, Vazirani S, Dracup K: **Evaluation of a Web-based education and counseling pilot program for older heart failure patients**. *Prog Cardiovasc Nurs* 2007, **22**(1):20-26.
64. Gustafson DH, Hawkins R, Boberg E, Pingree S, Serlin RE, Graziano F, Chan CL: **Impact of a patient-centered, computer-based health information/support system**. *Am J Prev Med* 1999, **16**(1):1-9.

65. Gustafson DH, Hawkins RP, Boberg EW, McTavish F, Owens B, Wise M, Berhe H, Pingree S: **CHESS: 10 years research and development in consumer health informatics for broad population, including the underserved**. *Int J Med Inf* 2002, **65**(3):169-177.
66. Gustafson DH, Hawkins R, McTavish F, Pingree S, Chen WC, Volrathonchai K, Serlin RC: **Internet-based interactive support for cancer patients: are integrated systems better?** *J Commun* 2008, **58**:238-257.
67. Helwig A, Lovelle A, Guse C, Gottlieb M: **An office-based internet patient education system: a pilot system.** *J Fam Pract* 1999, **48**(2):123-127.
68. Roberto AJ, Zimmerman RS, Carlyle KE, Abner EL: **A computer-based approach to preventing pregnancy, STD, and HIV in rural adolescents**. *J Health Commun* 2007, **12**:53-76.
69. Tetzlaff L: **Consumer informatics in chronic Illness.** *Journal of Am Med Inform Assoc* 1997, **4**(4):285-300.
70. Winzelberg A, Eppstein D, Eldredge K, Wilfley D, Dasmahapatra R, Dev P, Taylor C: **Effectiveness of an internet-based program for reducing risk factors in eating disorders**. *J Consult Clin Psychol* 2000, **68**(2):346-350.
71. **"Cyberchondriacs" on the Rise? Those who go online for healthcare information continues to increase** [http://www.harrisinteractive.com/NewsRoom/HarrisPolls/tabid/447/mid/1508/articleId/448/ctl/ReadCustom%20Default/Default.aspx]
72. **Canadian Internet Use Survey** [http://www.statcan.gc.ca/daily-quotidien/100510/dq100510a-eng.htm]
73. **Utilisation d'Internet au Québec en novembre 2011 [Internet use in Quebec on November 2011]** [http://blogue.cefrio.qc.ca/2011/11/utilisation-dinternet-au-quebec-en-novembre-2011/]
74. **National Institutes of Health: Grants and funding opportunities** [http://grants.nih.gov/grants/oer.htm]
75. Godin G, Côté J, Naccache H, Lambert LD, Trottier S: **Predictors of adherence to antiretroviral therapy: A one year longitudinal study**. *AIDS Care* 2005, **17**:493-504.
76. Côté J, Godin G, Ramirez P, Gagnon ML, Rouleau G: **Program development for enhancing adherence to antiretroviral therapy among persons living with HIV**. *AIDS Patient Care STDS* 2008, **22**(12):965-975.
77. Côté J, Ramìrez-Garcia P, Rouleau G, Saulnier D, Guéhéneuc YG, Hernandez A, Godin G: **A nursing virtual intervention : Real-time support for managing antiretroviral therapy**. *Comput Inform Nurs* 2011, **29**(1):43-51.
78. Bartholomew LK, Parcel GS, Kok G, Gottlieb NH: *Intervention mapping: Designing theory- and evidence-based health promotion programs.* Mountain View, CA: Mayfield Publishing Co; 2001.
79. Bartholomew LK, Parcel GS, Kok G, Gottlieb NH: *Planning health promotion programs: An intervention mapping approach.* San Francisco: Jossey-Bass; 2006.
80. Bandura A: *Self-efficacy: The exercice of control.* New York: Freeman; 1997.
81. Tuldrà A, Fumaz CR, Ferrer MJ, Bayés R, Arno A, Balagué M, Bonjoch A, Jou A, Negredo E, Parades R *et al*: **Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2000, **25**:221-228.

82. Godin G, Gagné C, Naccache H: **Validation of a self-reported questionnaire assessing adherence to antiretroviral medication**. *AIDS Patient Care STDS* 2003, **17**:325-332.
83. Justice AC, Holmes W, Gifford AL, Rabeneck L, Zackin R, Sinclair G, Weissman S, Neidig J, Marcus C, Chesney M *et al*: **Development and validation of a self-completed HIV symptom index**. *J Clin Epidemiol* 2001, **54**(12, supplement 1):S77-S90.
84. Badia X, Podzamczer D, Garcìa M, López-Lavid C, Consiglio E: **A randomized study comparing instruments for measuring health-related quality of life in HIV-infected patients. Spanish MOS-HIV and MQOL-HIV Validation Group. Medical Outcomes Study HIV Health Survey**. *AIDS* 1999, **13**(13):1727-1735.
85. Badia X, Podzamcer D, Casado A, López-Lavid C, M. G: **Evaluating changes in health status in HIV-infected patients: Medical Outcomes Study-HIV and Multidimensional Quality of Life-HIV quality of life questionnaires. Spanish MOS-HIV and MQOL-HIV Validation Group**. *AIDS* 2000, **14**(10):1439-1447.
86. Liang K, Zeger S: **Longitudinal data analysis using generalized linear models**. *Biometrics* 1986, **7**(1):13-22.
87. Bryk A, Raudenbush S, Congdon R (Eds.): *Hierarchical linear and nonlinear modeling with the HLM/2L and HLM/3L programs*. Chicago, IL: Scientific Software International; 1996.
88. Bennett GG, Glasgow RE: **The delivery of public health interventions via the Internet: actualizing their potential**. *Annu Rev Public Health* 2009, **30**:273-292.
89. Birnbaum MH: **Human Research and Data Collection via the Internet**. *Annu Rev Psychol* 2004, **55**:803-832.
90. Bull S, Lloyd L, Rietmeijer C, McFarlane M: **Recruitment and retention of an online sample for an HIV prevention intervention targeting men who have sex with men: the Smart Sex Quest Project**. *AIDS Care* 2004, **16**(8):931-943.
91. Nosek BA, Banaji MR: **E-Research: Ethics, security, design, and control in Psyhological Research on the Internet**. *J Soc Issues* 2002, **58**(1):161-176.
92. Smith MA, Leigh B: **Virtual subjects: Using the Internet as an alternative source of subjects and research envrionment**. *Beh Res Meth* 1997, **29**(4):496-505.
93. Gosling SD, Vazire S, Srivastava S, John OP: **Should we trust Web-based studies?** . *Am Psychol* 2004, **59**:93-104.
94. Beddows E: **The Methodological Issues Associated with Internet-Based Research**. *Int J Emerg Tech & Society* 2008, **6**(2):124-139.
95. Hewson C: **Conducting research on the internet**. *The Psychologist* 2003, **16**(6):290-293.
96. Michalak EE, Szabo A: **Guidelines for Internet Research: An pudate**. *Eur Psychol* 1998, **3**(1):70-75.
97. Paul J, Seib R, Prescott T: **The internet and clinical trials: Background, online resources, examples and issues**. *J Med Internet Res* 2005, **7**(1):e5.
98. Schubart JR, Stuckey HL, Ganeshamoorthy A, Sciamanna CN: **Chronic health conditions and Internet Behavioral Interventions**. *Comput Inform Nurs* 2011, **29**(2):TC9-TC20.
99. Bull S, Pratte K, Whitesell N, Rietmeijer C, McFarlane M: **Effects of an Internet-based intervention for HIV prevention: the Youthnet trials**. *AIDS Behav* 2009, **13**(3):474-487.

[i] *VIH-TAVIE stands for Virus de l'immunodéficience humaine–traitement assistance virtuelle infirmière et enseignement. In French, the acronym contains a wordplay rendered in English as "live your life".