Current HIV/AIDS Reports (2023) 20:502–512
https://doi.org/10.1007/s11904-023-00671-z

Digital Adaptive Behavioral Interventions to Improve HIV Prevention and Care: Innovations in Intervention Approach and Experimental Design

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Accepted: 6 October 2023 / Published online: 4 November 2023

Abstract

Purpose of Review Recent advances in digital technologies can be leveraged to adapt HIV prevention and treatment services to the rapidly changing needs of individuals in everyday life. However, to fully take advantage of these technologies, it is critical to effectively integrate them with human-delivered components. Here, we introduce a new experimental approach for optimizing the integration and adaptation of digital and human-delivered behavioral intervention components for HIV prevention and treatment.

Recent Findings Typically, human-delivered components can be adapted on a relatively slow timescale (e.g., every few months or weeks), while digital components can be adapted much faster (e.g., every few days or hours). Thus, the systematic integration of these components requires an experimental approach that involves sequential randomizations on multiple timescales.

Summary Selecting an experimental approach should be motivated by the type of adaptive intervention investigators would like to develop, and the scientific questions they have about its construction.

Keywords Adaptive interventions · Just-in-time adaptive interventions · Multimodality adaptive intervention · Sequential multiple assignment randomized trial (SMART) · Micro-randomized trial (MRT) · Hybrid experimental design (HED)

Introduction

The rapid growth, affordability, and acceptability of digital technologies can revolutionize behavioral interventions to improve HIV prevention and treatment, facilitating greater access, scalability, and impact. Innovations in information and communication technologies can be leveraged to adapt HIV-related behavioral interventions to the rapidly changing needs of individuals in everyday life. However, to fully take advantage of these technologies, it is critical to effectively integrate them with human-delivered components. This blending is critical because each modality holds different advantages and disadvantages. Advantages of digital components include relatively low dissemination costs, the capability to be administered anywhere and extend therapeutic contact beyond the clinic, saving providers' time, allowing participants to work at their own pace, saving traveling time and expenses, and reducing stigma [1]. Drawbacks include the need for certain resources (e.g., high speed internet or smartphone) and abilities (e.g., reading, writing, and digital literacy), and challenges to engagement (e.g., distractions and competing demands for the person's time and effort [2]). Human-delivered components have the advantage of facilitating therapeutic alliance and supportive accountability which can promote intervention engagement [3]. However, these components are often expensive and burdensome, involving challenges such as finding a provider, making child-care arrangements, and traveling time. Optimally integrating digital and human-delivered components has the potential to increase the impact and scalability of interventions for individuals with or at risk for HIV.

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A key challenge to optimizing the integration between human-delivered and digital components relates to the different timescales at which these components can be delivered and adapted [4•]. Adaptation is defined as the protocolized and evidence-based use of dynamic information about the individual to decide whether and how to intervene [5]. Here, 'protocolized' means that there is a clear and comprehensive description of how dynamic information about the person should be used in practice to make intervention decisions. This protocolization ensures that the adaptation process can be implemented and replicated with high fidelity.

Typically, digital components can be adapted on a relatively fast timescale (e.g., every day or every few hours), whereas human-delivered components can be adapted on a relatively slow timescale (e.g., every few weeks or months). Although people are equally capable of modifying their actions rapidly based on dynamic information, these modifications are rarely protocolized. Consider an adherence counseling session in which a provider may change their suggestions and/or questions rapidly in response to patient's reactions. For practical reasons (e.g., cognitive load and complexity), it would be highly challenging for this provider to follow a pre-specified protocol that describes how they should change their behavior during the session based on patient's reactions. Further, suppose the provider would like to encourage the patient whenever they take their medication. This would require monitoring the patient on a daily basis (to determine whether or not they took their mediation) and delivering an intervention (here, encouragement) frequently, outside of standard treatment settings. While practical constrains (e.g., time, geographical location, and cost) hinder the ability of human-delivered care to adapt intervention delivery rapidly in daily life, ongoing improvement in the performance, functionality, and adoption of digital technologies enable and accelerate these capabilities.

Thus, answering scientific questions about how to best blend human-delivered and digital intervention components requires trial designs that can accommodate the multiple timescales at which human-delivered and digital components can be adapted. The goal of this manuscript is to explain how the hybrid experimental design (HED) [4, 6•]—a new experimental approach involving sequential randomizations on multiple timescales—can be used to optimize the integration between digital and human-delivered intervention components for HIV prevention and treatment. We begin by explaining what adaptive interventions are, how they can be used to guide the adaptation of human-delivered components, and how they can be systematically optimized with an experimental approach that involves sequential randomizations. We then explain what just-in-time adaptive interventions (JITAIs) are, how they can be used to guide the adaptation of digital components on a faster timescale, and how they can be systematically optimized with an experimental approach that involves sequential randomizations on a similarly fast timescale. Finally, we explain what multimodality adaptive interventions (MADIs) are, how they can be used to guide the integration between human-delivered and digital components that are adapted on slow and fast timescales, and how they can be systematically optimized with HEDs.

The HED, as well as the other experimental designs described here, can be viewed as *optimization trials* as they are intended to empirically inform how to best assemble the components of interventions that adapt to the changing needs of individuals. The goal of an optimization trial is to construct an effective and resource-efficient intervention package [7]. The performance of this optimized package can then be tested with an evaluation trial—a traditional two-arm trial comparing the adaptive intervention package to a suitable control such as the standard or care [7].

Throughout, we use examples based on a completed study to inform the development of an adaptive intervention for improving antiretroviral therapy (ART) adherence for youth with HIV [8]. The details of this study are modified for illustrative purposes. Table 1 provides a summary of key terms and definitions. Table 2 summarizes the hypothetical trial designs used for illustration as well as published designs when available.

Adaptive Interventions

An adaptive intervention [12] is an intervention approach, namely, the specific details guiding the delivery of an intervention program in practice [7]. An adaptive intervention guides the *adaptation* of intervention components, where adaptation refers to the protocolized and evidence-based use of dynamic information about the individual to decide whether and how to deliver intervention-related services [5]. An adaptive intervention is not an experimental design—it does not involve random assignment of participants to experimental conditions because it is *not* intended to answer scientific questions. Rather, an adaptive intervention is intended to guide the adaptation of intervention components in practice, that is to provide a clear protocol that providers can use in practice to make intervention decisions.

Adaptive interventions typically guide the adaptation of human-delivered components, or other components that can be adapted on relatively slow timescales, such as every few weeks or months. For example, consider the hypothetical adaptive intervention in Fig. 1 for improving antiretroviral therapy (ART) adherence for youth with HIV [8]. First, youth are offered telephone support (i.e., daily phone calls from an adherence facilitator). Second, at month 3, non-responders (i.e., viral load $\geq$ 200 copies/mL) switch to incentivized text message support (i.e., daily personalized

Table 1 Key terms

Intervention approach	Experimental design
Standard adaptive intervention	Sequential multiple assignment randomized trial (SMART)
Baseline and time-varying information about the individual is used to decide whether and how to intervene. Involves adaptation on a slow timescale: intervention decisions are made every few weeks or months.	Experimental design providing the empirical basis for constructing a standard adaptive intervention. Involves sequential randomizations: each person may be randomized among intervention options more than once. Randomizations are on a slow timescale: they occur only a few times (typically 2–3) and the length of the time interval between randomizations is relatively long (e.g., a few weeks or months).
Just-in-time adaptive intervention (JITAI)	Micro-randomized trial (MRT)
Rapidly changing information about the individual's internal state and context is used to decide whether and how to intervene in real time, in daily life. Involves adaptation on a fast timescale: decisions are made every few days, hours, or minutes.	Experimental design providing the empirical basis for constructing a JITAI. Involves sequential randomizations on a fast timescale: each individual randomized to just-in-time intervention options hundreds or thousands of times and the length of the time interval between randomizations is relatively short (e.g., a few days, hours, and minutes).
Multimodality adaptive intervention (MADI)	Hybrid experimental design (HED)
Human-delivered and digital intervention components are integrated and adapted over time, on multiple timescales—slow and fast.	Experimental design providing the empirical basis for constructing a MADI. Involves sequential randomizations to different intervention components on multiple timescales—slow and fast.

adherence reminders with incentives for responding to the messaging; see [8]) whereas responders (i.e., viral load < 200 copies/mL) transition to a tapered intervention, where calls are reduced to 2 days per week. This intervention is adaptive because it uses dynamic information about the individual's response status to decide whether to switch or taper the intervention. The term 'tailoring variable(s)' is used to describe this information. In practice, the adaptation is a process that involves gathering information about the tailoring variable(s), using thresholds or levels of the tailoring variable(s) to differentiate between those who should be offered different intervention options (i.e., different types, intensities, tactics, or intervention modalities) and delivering the recommended option. This process is triggered at decision points, namely, points in time in which intervention decisions should be made. In the current example, there are decision points at program entry and at month 3.

The adaptation process is guided by the need to achieve proximal outcomes (i.e., the short-term goal of the adaptation) in order to achieve a distal outcome (i.e., the ultimate goal the intervention is intended to achieve). In the current example, the proximal outcome is ART adherence during the intervention and the distal outcome is month 12 viral suppression. Note that in adaptive interventions, the tailoring variable can be based on the proximal outcome measured at prior time points, but not necessarily. Useful tailoring variables are often those that help identify conditions that represent heightened susceptibility that precede the selected proximal outcome(s) [13]. Here, the assumption is that viral load ≥ 200 copies/mL at month 3 represents heightened susceptibility for continued medication nonadherence in the course of the intervention and subsequent failure to achieve viral suppression at month 12. Thus, more support for medication adherence is delivered to those who at month 3 have viral load ≥ 200 copies/mL.

The adaptation is motivated to improve the overall effectiveness and resource efficiency of the intervention. For example, the adaptation in Fig. 1 is intended to address early signs of non-response by switching to incentivized text message support. The assumption is that youth who show early signs of non-response require switching to a different intervention approach to achieve month 12 viral suppression. By switching early non-responders to a different type of intervention, the number of individuals who achieve long-term viral suppression can be increased, thus enhancing the overall effectiveness of the intervention. Another assumption is that those who show early signs of response do not require more intense and potentially costly or burdensome forms of support to succeed. By stepping down the intensity of the intervention for early responders, this adaptation is designed to minimize the delivery of unnecessary or potentially harmful treatment, thus increasing the resource efficiency of the intervention.

In many cases, investigators have scientific questions about how to optimize, namely, how to systematically build an effective and resource-efficient [7], adaptive intervention. Depending on the scientific questions, different trial designs can be considered. Below, we focus on the sequential multiple assignment randomized trial (SMART [14, 15])—a trial design intended to collect data for answering scientific questions about the selection and adaptation of intervention components at two or more decision points in the adaptive intervention of interest.

Table 2 Summary of hypothetical and published designs

Study	Trial design	Randomization timescale	Adaptive intervention to be developed	Scientific questions	Non-response criteria
Belzer et al. (2018) [8]	SMART	Slow	Standard	(a) Begin with phone support or text messaging for adherence? (b) For responders at month 3, taper support or no additional support? (c) For non-responders at month 3, follow with incentivized telephone support or incentivized text messaging?	Unsuppressed at month 3
Abuogi et al. (2023) [9]	SMART	Slow	Standard	(a) Begin with electronic navigation or with standard of care? (b) For non-responders during the first year, augment with (i) intensified counseling; (ii) conditional incentives; or (iii) in-person peer navigation?	Unsuppressed OR missed visits during first year
Edelman et al. (2021) [10]	SMART	Slow	Standard	(a) Begin with nicotine replacement therapy (NRT) or NRT + contingency management (CM)? (b) For non-responders at 12 weeks, switch to a different medication or continue NRT and intensify the CM?	Not achieving 7-day self-reported smoking abstinence confirmed by exhaled carbon monoxide (eCO) at 12 weeks
Van Heerden et al. 2023 [11]	SMART	Slow	Standard	(a) Begin with or without lottery incentives for linkage to care? (b) For non-responders at month 6, (i) continue; (ii) add smart locker medication pick up; or (iii) add home delivery of medications?	Unsuppressed OR not engaged in care at 6 months
Hypothetical	MRT	Fast	Just-in-Time	For non-responders to current day adherence message, deliver or do not deliver an inspirational message?	Not texting back in response to current day adherence message
Hypothetical	HED	Fast and Slow	Multimodality	(a) For non-responders to current day adherence message, deliver or not deliver an inspirational message? (b) Does starting with telephone (vs. text message) support amplify the benefits of delivering (vs. not delivering) an inspirational message?	Not texting back in response to current day adherence message (fast timescale); Unsuppressed at 3 months (slow timescale)

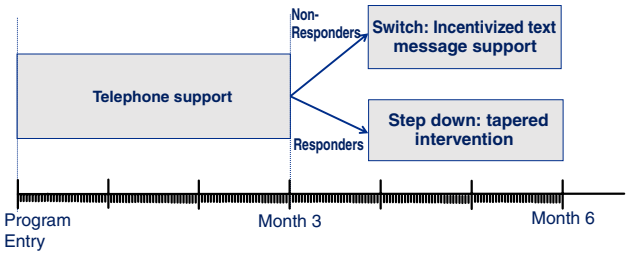

Fig. 1 Hypothetical example of an adaptive intervention for improving ART adherence for youth with HIV

SMART design in Fig. 2 [8], whereby youth with HIV are first randomly assigned (0.5 probability) to either daily telephone support for 3 months or daily text message support for 3 months. Second, at month 3, non-responders (i.e., viral load ≥ 200 copies/mL) are randomly assigned again (0.5 probability) to either incentivized telephone support or incentivized text message support, whereas responders (i.e., viral load < 200 copies/mL) are randomly assigned to either a tapered intervention, where the intensity of calls/texts are reduced to 2 days per week, or the standard of care where no intervention calls/texts are delivered. The

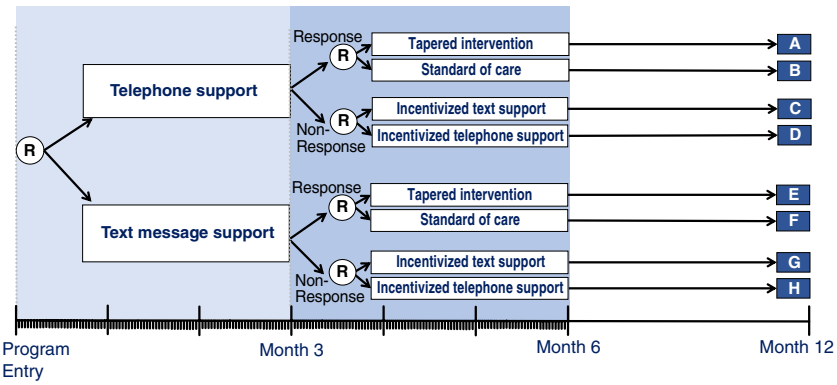

Fig. 2 An example SMART to empirically inform an adaptive intervention for improving ART adherence for youth with HIV

The SMART

The SMART [14, 15] is an experimental design to develop an adaptive intervention. It involves sequential randomizations, meaning that some or all study participants can be randomly assigned to intervention options multiple times during the trial. Each stage of randomizations in the SMART corresponds to a decision point in the adaptive intervention of interest, for which there are scientific questions about whether, how and under what conditions to intervene. For example, suppose that in the process of developing the adaptive intervention described above for improving ART adherence, investigators pose three scientific questions: first, at program entry, is it beneficial (in terms of month 12 viral suppression) to start with telephone support or with text message support (i.e., daily personalized but automated adherence messages)? Second, at month 3, is it more beneficial (for month 12 viral suppression) to offer incentivized telephone support (i.e., provide monetary incentives for answering the cell phone support call) or incentivized text message support (i.e., provide monetary incentives for responding to adherence text messages) to youth who show early signs of non-response? Third, at month 3, is it more beneficial (for month 12 viral suppression) to step down youth who show early signs of response to a tapered intervention or to the standard of care where no intervention calls/text are delivered? These questions can be answered with the primary distal outcome is change in viral suppression from baseline to month 12. Although the SMART in Fig. 2 leads to 8 experimental conditions (A–H) it has been shown that this design is highly efficient in achieving statistical power for primary questions about optimizing adaptive interventions [14, 16, 17•]. The sequential randomizations in the SMART enable investigators to combine multiple experimental cells in different ways to answer multiple scientific questions, such as the three questions posed earlier (see details in [4, 5, 18]). For example, the first question can be answered by comparing the primary outcome across all the conditions in which participants were offered daily telephone support initially (Fig. 2(A)–(D)) to the primary outcome across all the conditions in which participants were offered the text message support initially (Fig. 2(E)–(H)). This comparison, which involves leveraging outcome data from the entire sample, can be viewed as the main effect of the choice of initial component, averaging over the subsequent components for non-responders and responders [17, 19].

Recent years have seen rapid growth in research using the SMART to optimize adaptive interventions for HIV prevention and treatment. This includes SMARTs to optimize adaptive interventions for improving retention and viral suppression among adolescents and young adults with HIV in Kenya [9], treating tobacco use disorder in persons with HIV [10] and delivering ART to South Africans with HIV [11].

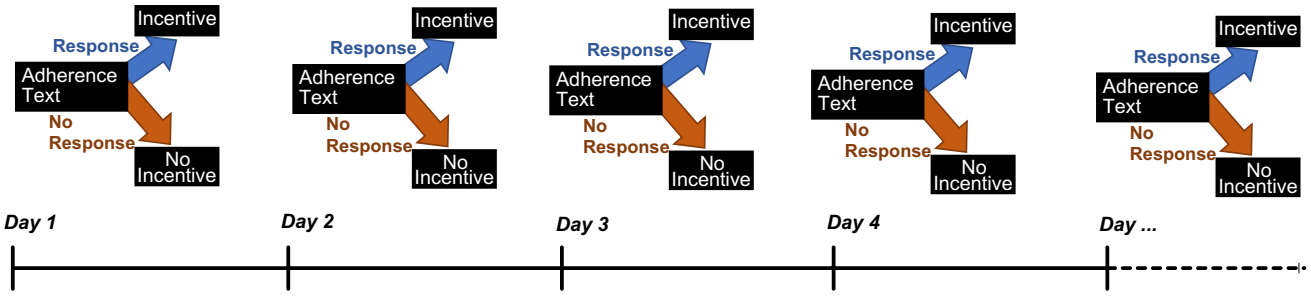

Fig. 3 Hypothetical example of an incentivized text message JITAI to improve ART adherence for youth with HIV

Just-In-Time Adaptive Interventions (JITAI)

A JITAI [13, 20] is an intervention approach that guides the adaptation of just-in-time intervention components, namely components that can be delivered in-the-moment during daily life. These components are typically digital and can be adapted on relatively fast timescales, such as every few days, hours, minutes or seconds. Similar to adaptive interventions, JITAIs are not intended to answer scientific questions by testing effects. Rather, they are intended to provide a protocol that can be used in practice (here, by the digital tool) to make intervention decisions. As an example, consider the hypothetical incentivized text messaging JITAI in Fig. 3. Every day, a text message is delivered to remind the participant to take their medication. Participants are asked to text back and indicate whether they took their ART medications. If the participant responded to the message (i.e., texted back regardless of their answer), another message is delivered immediately, informing the participant that they have earned a small monetary incentive ($1). Otherwise, an incentive message is not delivered. This intervention is adaptive because it uses dynamic information about the individual's response to the adherence message to decide whether to deliver an incentive message. The adaptation occurs on a fast timescale because the goal is to address conditions that change relatively fast over time. Specifically, the decision whether to deliver an incentive message is made every day (i.e., there are daily decision points in this JITAI) because the goal is to address non-response to the adherence message which can happen every day.

Similar to standard adaptive interventions, the adaptation in JITAIs is intended to improve overall effectiveness and resource efficiency. Specifically, to improve overall effectiveness, the adaptation in JITAIs is designed to address conditions that represent vulnerability (i.e., risk) to an adverse proximal outcome (e.g., non-response to an adherence message may represent risk for same day ART non-adherence) and/or opportunity to promote a desired proximal outcome (e.g., response to an adherence message may be an opportunity to reinforce this behavior by delivering an incentive and thus improve next day response to the adherence message). By preventing adverse proximal outcomes and/or capitalizing on windows of opportunity for positive change in everyday life, the adaptation increases the likelihood that participants ultimately benefit from the intervention [20]. To improve resource efficiency, the adaptation in JITAIs is designed to avoid delivering an intervention when unnecessary or potentially harmful. This is done by delivering interventions only when needed (i.e., when states of vulnerability and/or opportunity occur), and only when the individual is receptive to the intervention. Receptivity is defined as conditions in which the individual is likely to effectively engage with the specific intervention [21]. Here, effective engagement refers to investing physical, cognitive, and emotional energies in a way that is likely to bring about a prespecified desirable outcome while minimizing harm. For example, suppose participants are unlikely to effectively engage with the adherence message while driving (in which case paying attention to the message may have adverse consequences) and/or when they are at work (e.g., due to confidentiality concerns). In this case, the JITAI in Fig. 3 may be modified to deliver an adherence message only when the person is not driving and not at work.

Recently, there has been growing interest in developing JITAIs for HIV prevention and treatment. Examples include a JITAI that delivers behavioral feedback and goal attainment insights based on real-time predictors of HIV risk behaviors [22]; a JITAI for sexual minority men with HIV that triggers brief mindfulness-based activities based on self-reported stress [23]; and a JITAI for mitigating HIV risks in youth experiencing homelessness, that delivers prevention messages based on the participant's responses to brief assessments several times per day [24]. This research highlights many scientific questions about how to best construct effective and resource-efficient JITAIs. Below, we discuss the micro-randomized trial (MRT [25, 26])—a trial design intended to collect data for answering scientific questions about the selection and adaptation of just-in-time intervention components.

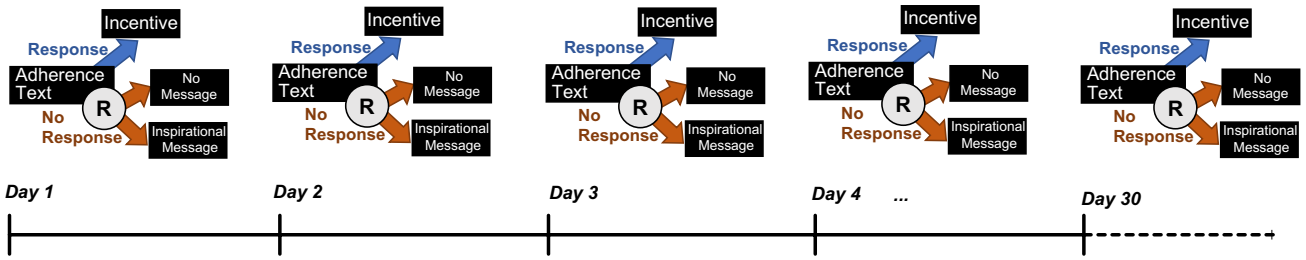

Fig. 4 Hypothetical MRT to inform an incentivized text message JITAI for improving ART adherence among youth with HIV

The MRT

The MRT [25, 26] is an experimental design involving sequential randomizations on a relatively fast timescale. Each stage of randomization corresponds to a decision point in the JITAI of interest, in which there are scientific questions about the selection and adaptation of just-in-time components. This means that the same person can be randomized many times, and the length of the time interval between stages of randomizations is relatively short. For example, suppose that in developing the JITAI in Fig. 3, investigators pose the following question: is it beneficial on average (in terms of increasing next-day response to the adherence message) to deliver or not deliver an inspirational message when the participant does not respond to the adherence message? The rationale is that an inspirational message may serve as a cue for action while generating positive emotions which may increase the likelihood of responding to the adherence message on the next day (see details in [27]). The MRT in Fig. 4 can be used to answer this question. This MRT employs random assignments daily over 3 months: every day an adherence message is delivered to remind the participant to take their medication. If the participant responds to the message, an incentive message is delivered, informing them that they have earned a small monetary incentive. If the participant does not respond within 2 hours, they are randomly assigned to either an inspirational message that contains song lyrics or celebrity quotes [27] or no inspirational message. The sequential randomizations in the MRT enable investigators to leverage within-person and between-person contrasts in the proximal outcome to answer scientific questions about how to best build a JITAI. For example, the question motivating the MRT in Fig. 4 can be answered by comparing two probabilities for current-day non-responders: (a) the probability of response to next-day adherence message when an inspirational message was delivered and (b) the probability of response to next day adherence message when an inspirational message was not delivered. This difference can be estimated by pooling data across all decision points in which participants did not respond to the adherence message, as well as across all study participants. Although the MRT is a relatively new experimental approach, it is increasingly employed to empirically inform the development of JITAIs targeting various chronic disorders (see examples in [28–30]). However, often investigators have scientific questions about how to best integrate a digital JITAI with human-delivered components that are adapted on a much slower timescale. These questions concern how to construct a multimodality adaptive intervention, which we define in the next section.

Multimodality Adaptive Interventions (MADIs)

The multimodality adaptive intervention (MADI [4, 6•]) is an intervention approach that guides how human-delivered and digital components should be integrated and adapted on multiple timescales—slow and fast. It can be viewed as an integration between a standard adaptive intervention and a JITAI. For example, consider the adaptive intervention in Fig. 1 and suppose that the incentivized text messaging offered to non-responders at month 3 follows the JITAI described in Fig. 3. Specifically, youth are first offered telephone support, and then at month 3, non-responders switch to incentivized text message support whereas responders step-down to a tapered intervention. Participants assigned to the incentivized text support are sent an adherence message every day; if they respond to this message an incentive message (i.e., a message informing them that they have earned a small monetary incentive) is delivered immediately, and otherwise an incentive message is not delivered. This intervention (Fig. 5) integrates human-delivered (telephone support) and digital components (text messaging) that are adapted on different timescales: slow (3 months after program entry) and fast (every day). Notice that the human-delivered components (i.e., telephone support and the tapered intervention) are adapted on a relatively slow timescale, whereas the digital components are adapted both on a slow timescale (i.e., the incentivized text support) and on a fast time scale (i.e., the just-in-time incentive message

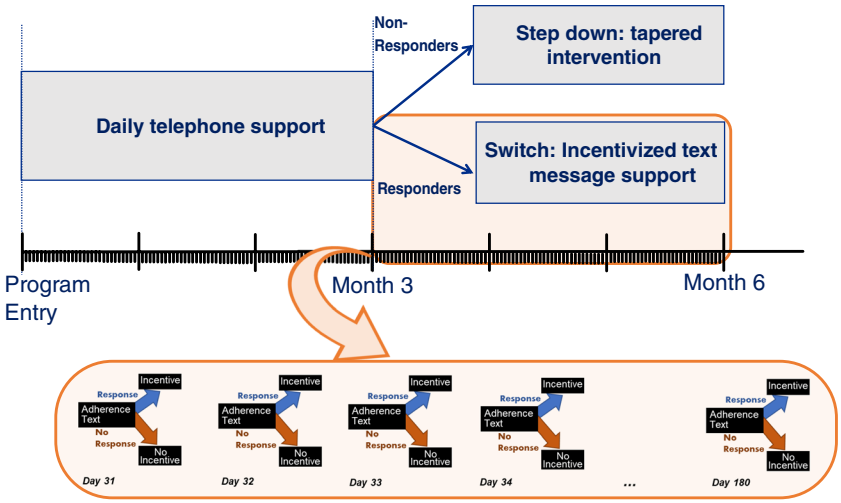

Fig. 5 Hypothetical example of a multimodality adaptive intervention (MADI) to improve ART adherence for youth with HIV

within the incentivized text support). Specifically, the incentivized text support is a digital component that is adapted at month 3 (i.e., the decision about whether to deliver this component is made at month 3). However, within this component, there is a just-in-time component (incentive message) that is adapted daily (i.e., decisions about whether to deliver this component are made daily).

Like standard adaptive interventions and JITAIs, the adaptation in MADIs is intended to improve overall effectiveness and resource efficiency. To improve overall effectiveness, the adaptation in MADIs leverages human-delivered and digital components to address conditions that change both slowly and rapidly. To achieve resource efficiency, the adaptation in MADIs is designed to avoid delivering an intervention when unnecessary or potentially harmful.

Since MADIs involve adaptation of human-delivered and digital components on multiple timescales, answering scientific questions about how to best construct these interventions requires an experimental approach that accommodates sequential randomizations on multiple timescales. Below, we discuss the hybrid experimental design (HED)—a trial design intended to collect data for answering scientific questions about the selection and adaptation of intervention components on multiple timescales.

The HED

The HED [4, 6•] is an experimental design that involves sequential randomizations on multiple timescales—slow and fast. Each stage of randomization corresponds to a decision point in the MADI of interest, in which there are scientific questions about the selection and adaptation of components relevant to that decision point. For example, suppose that in developing the MADI in Fig. 5, investigators pose the following questions about how to best deliver the incentivized text support for non-responders at month 3: (a) is it beneficial on average (in terms of increasing next-day response to the adherence message) to deliver or not deliver an inspirational message when the participant does not response to the adherence message; and (b) do these benefits amplify for those starting with telephone support (vs. text message support)? These questions can be answered with the HED in Fig. 6, which integrates the SMART in Fig. 2 with the MRT in Fig. 4. Specifically, this HED employs random assignments on 2 timescales. The slow timescale randomizations occur at program entry and 3 months later. They include assigning participants at program entry to either a human-delivered (telephone support) or a digital component (text message support), and then at month 3 assigning non-responders to a subsequent component that is either human-delivered (incentivized telephone support) or digital (incentivized text support), whereas responders are assigned to either a tapered intervention or the standard of care. The fast timescale randomizations occur daily, only among month 3 non-responders assigned to the incentivized text support. Here, those who do not respond to the daily adherence message are randomly assigned to either an inspirational message or no inspirational message.

The sequential randomizations in the HED enable investigators to combine experimental cells in different ways to answer multiple questions about how to best construct a MADI. For example, the first question motivating this HED can be answered by comparing two probabilities among those assigned to the incentivized text messaging: (a) the probability of response to next-day adherence message when an inspirational

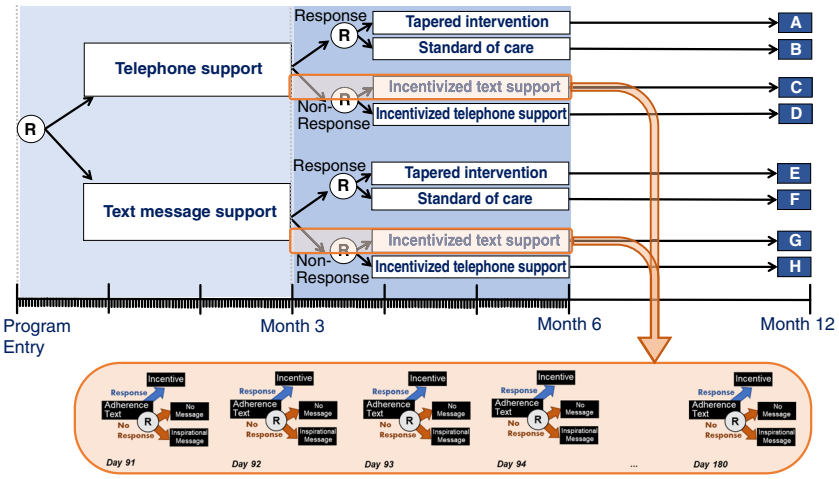

Fig. 6 An example HED to inform a MADI for improving ART adherence among youth with HIV

message was delivered to current day non-responders and (b) the probability of response to next-day adherence message when an inspirational message was not delivered to current day non-responders. This is the average proximal main effect of delivering (vs. not delivering) an inspirational message to those who do not respond to the adherence message on a given day. The second question can be answered by comparing this average proximal effect between those who started with daily telephone support and those who started with text message support. This corresponds to an interaction between delivering (vs. not delivering) an inspirational message to those who do not respond to the adherence message, and starting with human support (vs. text message support). While these effects (main and interaction) can be estimated with only a subset of study participants (i.e., those assigned to incentivized text support), both leverage within-person and between-person contrasts in the proximal outcome and thus may be detected with acceptable power even with a reasonable total sample size for the trial (e.g., N=190 as in [8]).[1] Other scientific questions that can be answered with the HED, and approaches for analyzing the data to answer them and for planning sample size for HEDs, are described in [4•] and [6•]. A HED is currently underway to develop a MADI to address medication adherence and alcohol use in youth with HIV [32].

[1] For example, with 190 participants enrolled in the study, and 50% response rate at month 3, 47 participants would be assigned to the incentivized text support and will be micro-randomized daily over 90 days (if they do not respond to the adherence message). This sample size can provide 81% power to detect a constant proximal effect of (at least) 20% greater likelihood of next-day response when delivering (vs. not delivering) an inspirational message on a given day. Here, we assume a linear downward trend in the rate of current-day response to the adherence message, from 70 to 30%, and a constant rate of 30% next-day response to the adherence message when an inspirational message is not delivered on the current day [31].

Conclusion

Adaptive interventions hold tremendous potential for improving the effectiveness and resource efficiency of interventions for preventing and treating HIV. In addition, these interventions contribute to achieving health equity in three respects. First, they enact a paradigm shift from a one-size-fits-all approach to matching the type of intervention to the unique and changing needs of each individual. Second, they address heterogeneous responses to intervention, thus increasing the number of individuals who benefit from an intervention program. Finally, they are explicitly designed to use scarce resources strategically to enhance effectiveness, reach, scalability, and implementation of services. Still, several limitations offer important directions for future research. Here, we highlight three challenges and opportunities.

First, suboptimal engagement remains a major barrier that undermines the potential of digital technologies to effectively deliver adaptive interventions [2]. While human-delivered support can be blended with digital components to improve engagement, the tradeoff is often higher cost, efforts and burden. More work is needed to not only systematically investigate how to best integrate, sequence, and adapt digital and human-delivered components so as to maximize effectiveness with minimal cost, efforts and burden, but also to develop new non-monetary and low burden strategies for promoting engagement in digital components [27].

Second, tailoring variables are key elements in any adaptive intervention. A tailoring variable is the information used to decide whether and how to intervene [5, 12]. This means that for information to be considered as an effective tailoring variable, it must be useful in differentiating between individuals who need one type of intervention and those who need an alternative. Investigators who are planning to develop a new adaptive intervention may

have many scientific questions about how to best construct a tailoring variable. These questions include which variables to use, when to measure them, when to make decisions based on these variables and how to make decisions based on these variables (i.e., what cutoff of levels to use in order to decide which intervention option to deliver). New experimental approaches and analytic methods are needed to help investigators address these questions efficiently when constructing tailoring variables for various types of adaptive interventions.

Finally, the SMART, the MRT, and the HED can take on various forms depending on the scientific questions motivating the study. For example, if there are no open scientific questions about how to best address the needs of responders in an adaptive intervention (see [33, 34]), the SMART can re-randomize only non-responders to subsequent options. If there are no scientific or practical reasons to restrict the delivery of just-in-time components in a JITAI (see [27]), the MRT can micro-randomize individuals at all decision points instead of only under specific states and/or context. If just-in-time components can be delivered to all participants throughout the entire duration of a MADI [4•, 6•], the HED can micro-randomize all participants (rather than a specific subgroup as in Fig. 6) over the course of the entire intervention duration (rather than starting at month 3 as in Fig. 6). New organizing frameworks are needed to guide investigators in selecting an appropriate experimental design based on the type of adaptive intervention they would like to develop, and the scientific questions they have about how to best construct this intervention.

Acknowledgements The authors would like to thank Dr. John J. Dziak for his helpful comments and advice, as well as Drs. Marvin Belzer and Karen MacDonell, chair and co-chair of the SMART study, ATN Protocol 144.

Funding Inbal Nahum-Shani was funded by National Institutes of Health grants: P50 DA054039, P01 AA029547, U01 CA229437, and R01 DA039901. Sylvie Naar was funded by National Institutes of Health grants: P01 AA029547 and U19 HD089875.

Declarations

Conflict of Interest Inbal Nahum-Shani declares that she has no conflict of interest. Sylvie Naar declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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