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EVIDENCE-BASED DECISION SUPPORT IN HIV/TB CARE

Designing treatment, monitoring, and assessment support for care providers

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ABSTRACT

Introduction: HIV and tuberculosis (TB) coinfection, which is a major challenge for healthcare systems worldwide, requires effective strategies to support care providers in applying best clinical evidence in making treatment decisions about the care of individual patients. Clinical decision support (CDS) systems have the potential to facilitate the implementation of evidence-based guidelines in clinical practice.

Aim: The aim of this thesis was to explore how a CDS system could be designed to support the adoption of evidence-based guidelines in the treatment of HIV-related TB.

Study design: The HIV outpatient clinic at the Karolinska University Hospital, Huddinge, Stockholm, was the setting for a user-centered design approach structured in three phases: contextual analysis (Studies I and II), design (Study III), and evaluation (Study IV). Study I explores care providers' challenges and requirements; Study II, which describes sociodemographic and clinical characteristics of patients in this setting, analyzes the factors associated with anti-TB treatment success as well as adverse drug reactions; Study III proposes a CDS framework of drug therapy recommendations that is applied to HIV-related TB treatment guidelines; Study IV formatively evaluates the conceptual design of a CDS prototype that is based on the framework developed in Study III.

Methods: In Study I, the contextual analysis is based on observations and interviews. Study II analyses patient treatment outcomes in the research setting between the years 1987 to 2010 (inclusive). Study III presents the design that is based on prototyping and guideline modeling. Study IV uses focus groups of physicians and nurses in the evaluation of the design.

Results: The contextual analysis revealed challenges related to the complexity of HIV-related TB treatment (Studies I and II). Because the care providers thought they lacked sufficient experience with HIV/TB drug therapy, they sought improved support tools and structures (Study I). Combined HIV and TB treatment was related to treatment success, but was also associated with adverse drug reactions (Study II). The design phase applied the eviTMA (evidence-based Treatment, Monitoring, and Assessment) framework to model HIV-related TB treatment guidelines. This resulted in a CDS prototype that models alternative drug therapy options, their expected effects, and recommended monitoring routines (Study III). The care providers identified several potential benefits of the eviTMA CDS prototype including support for decision making, collaboration, and quality improvement work (Study IV). Identified concerns that need to be addressed in future include the risk of overdependence on CDS, increased workload, and aspects related to the implementation and maintenance of a CDS system (Study IV).

Conclusions: The main contribution of this thesis is the eviTMA CDS framework designed to support care providers in the adoption of evidence-based drug therapy recommendations. The framework was evaluated in a CDS prototype for HIV-related TB treatment. Application to other conditions was desired by care providers and should be explored in future.

LIST OF PUBLICATIONS

1. **Wannheden C**, Westling K, Savage C, Sandahl C, Ellenius J. HIV and tuberculosis coinfection: A qualitative study of treatment challenges faced by care providers. Int J Tuberc Lung Dis. 2013 Aug 1;17(8):1029–35.

2. **Wannheden C**, Norrby M, Berggren I, Westling K. Tuberculosis among HIV-infected patients in Stockholm, Sweden, 1987–2010: Treatment outcomes and adverse reactions. Scand J Infect Dis. 2014 Feb 11;46(5):331-339.

3. **Wannheden C**, Hvitfeldt Forsberg H, Westling K, Ellenius J. Modeling evidence-based drug therapies: the eviTMA clinical decision support framework applied to HIV/TB care. Manuscript.

4. **Wannheden C**, Eftimovska E, Westling K, Ellenius J, Sandahl C, Hvitfeldt Forsberg H. Qualitative evaluation of the eviTMA clinical decision support model applied to HIV/TB care. Manuscript.

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ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ADI	AIDS-Defining Illness
cART	Combined Antiretroviral Therapy
CDM	Critical Decision Method
CDS	Clinical Decision Support
CIG	Computer-Interpretable Guideline
CPG	Clinical Practice Guideline
CTA	Cognitive Task Analysis
EBM	Evidence-Based Medicine
EHR	Electronic Health Record
eviTMA	evidence-based Treatment, Monitoring, and Assessment
GUI	Graphic User Interface
HIV	Human Immunodeficiency Virus
ICT	Information and Communication Technology
IRIS	Immune Reconstitution Inflammatory Syndrome
IQR	Interquartile Range
MDR-TB	Multi-Drug Resistant TB
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
OR	Odds Ratio
PI	Protease Inhibitor
TB	Tuberculosis
TNM	Task-Network Model
UML	Unified Modeling Language
UTAUT	Unified Theory of Acceptance and Use of Technology
XDR-TB	Extensively Drug-Resistant TB

1 INTRODUCTION

1.1 HIV-RELATED TB

1.1.1 The burden of disease

HIV-related tuberculosis is a major challenge for global health. The World Health Organization (2013b) reports that HIV-infected individuals are about 30 times more likely to develop active tuberculosis (TB) disease than individuals without HIV. TB is the most common presenting illness and the leading cause of death in HIV-infected individuals. The following global statistics are from 2012: approximately 35.3 million people had HIV; 1.1 million new cases of HIV-related TB were diagnosed; and 320,000 deaths from HIV-related TB were recorded (World Health Organization, 2013b).

In comparison to other countries, Sweden's number of identified cases of HIV and TB is one of the lowest. Figures reported by the Swedish Institute for Communicable Disease Control (2013) show that the prevalence of HIV in Sweden is less than 0.1% of the population. The following statistics are from 2012: approximately 6,200 patients were registered with HIV-infection; 441 cases of HIV were reported (incidence 5 cases/100,000 inhabitants); and 645 cases of TB were reported (incidence 6.8 cases/100,000 inhabitants) (Swedish Institute for Communicable Disease Control, 2013). However, the number of individuals with TB has steadily increased since 2003. Surveillance data on the coinfection of HIV and TB are not available in Sweden because incident cases are reported anonymously. To increase case detection of HIV-related TB, HIV testing is offered to all patients with suspected TB disease (National Board of Health and Welfare, 2009).

1.1.2 Treatment of HIV-related TB

The treatment of HIV-related TB requires polypharmacy in which combination drug regimens for both HIV and TB are used. Because antiretroviral therapy has evolved rapidly, more than 20 antiretroviral drugs have been licensed since the emergence of the HIV epidemic (Palmisano & Vella, 2011; Arribas & Eron, 2013).

In 1995 and 1996, when highly potent combination antiretroviral therapy (cART) was introduced, an immediate reduction in morbidity and mortality due to AIDS was observed (Palella et al., 1998). The reduction in mortality was sustained and the proportion of AIDS-related deaths decreased (Palella et al., 2006). The introduction of cART has also led to reduced TB morbidity (Lodi et al., 2013) and mortality (Abdool Karim et al., 2010). HIV has become a chronic disease, which has led to new questions about the optimal choice, timing, and duration of antiretroviral therapy (Palmisano & Vella, 2011).

The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents (2013) recommends the same anti-TB treatment for HIV-infected patients and for patients without HIV. These recommendations are consistent with the guidelines issued by the European AIDS Cinical Society (2014), as well as by the Swedish guidelines (National Board of Health and Welfare, 2009; Referensgruppen för antiviral terapi, 2014).

1.1.2.1 Standard TB regimen

The standard treatment for drug-susceptible TB is a two-month intensive phase with four drugs (rifampicin or rifabutin, isoniazid, pyrazinamide, and ethambutol), followed by a four-month continuation phase with two drugs (rifampicin or rifabutin, and isoniazid) (Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents, 2013). Ethambutol can be discontinued when the susceptibility to rifampicin and isoniazid has been confirmed.

1.1.2.2 Recommended combination regimens for HIV and TB

Combined treatment for HIV and TB with cART is recommended for all HIV-infected TB patients, although the timing of cART initiation depends on the patient's immune status (European AIDS Cinical Society, 2014). The two recommended ways to use cART are the following: 1) an antiretroviral regimen based on efavirenz, which is a non-nucleoside reverse transcriptase inhibitor (NNRTI), combined with a rifampicin-based anti-TB regimen; and 2) a protease inhibitor (PI) based regimen combined with a rifabutin-based anti-TB regimen (Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents, 2013; Referensgruppen för antiviral terapi, 2014). The former is preferred. If there are no other options, the following antiretroviral drugs should be used, although with caution: raltegravir, maraviroc, or enfuvirtid (Referensgruppen för antiviral terapi, 2014).

1.1.3 Treatment challenges

While combined treatment of HIV and TB enhances patient survival chances, there are many challenges with this treatment.

There are overlapping drug toxicities as well as drug-drug interactions between antiretroviral drugs and anti-TB drugs (Arbex, de Castro Lima Varella, de Siqueira, & de Mello, 2010). The main interactions are between the anti-TB drugs rifampicin and rifabutin and antiretroviral drugs, in particular PIs (Baciewicz, Chrisman, Finch, & Self, 2008). Patients on combined treatment have an increased risk of adverse events (Dos Santos et al., 2013; Dean et al., 2002).

Another challenge is the risk of the immune reconstitution inflammatory syndrome (IRIS), which is a paradoxical reaction that can result in clinical worsening of TB due to the enhancement of the patient's immune response when cART is administered (Lawn, Bekker,

& Miller, 2005). Early initiation of cART is associated with increased survival, but it has also been shown to increase the risk of IRIS (Abdool Karim et al., 2010; Havlir et al., 2011; Blanc et al., 2011). The optimal dosage and duration of anti-TB treatment as well as the proper timing of cART have been identified as major unresolved questions in the treatment of HIV-related TB (Khan et al., 2010).

TB relapse and drug resistance, which are mainly the result of non-adherence to treatment, also pose major challenges (Aaron et al., 2004). A substantial increase in multidrug resistant TB (MDR-TB) and in extensively drug-resistant TB (XDR-TB) has been observed in recent years (World Health Organization, 2013a).

Although several studies explore patients' perceptions of anti-TB treatment, only a few studies explore the perceptions of care providers (Watkins & Plant, 2005). The need to improve our knowledge and expertise related to anti-TB treatment by care providers has been reported in both low- and high-incidence settings (Moro et al., 2005; van der Werf, Langendam, Huitric, & Manissero, 2012). Furthermore, some studies report variations in adherence to HIV/TB guidelines and quality of care (Lee, Lobato, Buskin, Morse, & Costa, 2006; Chung, Chang, & Guo, 2007; Saraceni et al., 2011). Generally, we need to know more about the challenges care providers face. Such knowledge would help us advance the development and implementation of successful strategies to support evidence-based care in HIV-related TB treatment.

1.2 EVIDENCE-BASED CARE

Evidence-based medicine, which emerged in the 1990s, has been defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996, p. 1). It is estimated on average, there is a nine-year gap from the publication of evidence-based medical findings in reviews, papers, and textbooks to their implementation in clinical practice (Balas & Boren, 2000).

1.2.1 Clinical practice guidelines

Clinical practice guidelines (CPGs) support the dissemination of medical evidence. The purpose is to enhance the translation of research into practice, to reduce inappropriate practice variation, and to improve quality and safety in healthcare (Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, 2011). Such guidelines were first defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (Field & Lohr, 1990, p. 38). Recently, the CPGs definition was refined to better reflect the current emphasis on rigor, transparency, and evidence:

> Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review

> of evidence and an assessment of the benefits and harms of alternative care options. (Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, 2011, p. 4)

Several organizations have proposed standards, for the development, quality assessment, and implementation of guidelines. The Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines (2011) calls for transparency, more public involvement in the development process, as well as a standard format for presenting recommendations. The Guidelines International Network (G-I-N) proposes a set of minimum standards for the development of high-quality and trustworthy guidelines (Qaseem et al., 2012). They suggest criteria for the composition of the guideline development group and the development process, the representation of recommendations, as well as criteria for guideline appraisal, maintenance, and disclosure. The G-I-N collaborates with the Duodecim Medical Publications Ltd, which provides concise evidence summaries that are maintained in the Evidence-Based Medicine Guidelines (EBMG) collection ("Duodecim Medical Publications Ltd." 2014). Duodecim also maintains the Evidence-Based Medicine electronic Decision Support (EBMeDS) system, which can be integrated with electronic health records (EHRs) and provide active guideline support through alerts and reminders (Nyberg, 2012).

A number of tools have been developed to support guideline development, appraisal, and implementation. The *Appraisal of Guidelines, Research, and Evaluation* (AGREE) Collaboration has developed the AGREE II instrument that aims to assess the quality of guidelines and to support guidelines development, with a focus on methodological issues (Brouwers et al., 2010). The Instrument for GuideLine Implementability Appraisal (GLIA) evaluates the implementability of guidelines and identifies possible related barriers (Shiffman et al., 2005). This instrument is intended for guideline developers and for guideline users. According to Shiffman et al., implementability refers to the ease with which guideline recommendations can be implemented. Recommendations must clearly convey what should be done (executability) and under what conditions (decidability) (Shiffman et al., 2005). One of the dimensions of the GLIA is computability, which can be useful for evaluating implementability in a clinical decision support system. BRIDGE-Wiz is a software tool, developed to facilitate the development of guidelines (Shiffman, Michel, Rosenfeld, & Davidson, 2011), that offers guideline developers clear, transparent, and implementable recommendations. For example, by limiting the number of verb options, guideline developers can reduce ambiguity and vagueness in their recommendations.

1.2.2 Barriers to guideline adoption

The dissemination of high-quality CPGs does not guarantee their adoption in clinical practice. Successful adoption of CPGs depends on how well they meet the needs and preferences of individual users (e.g., physicians and nurses) and on the clinical context

(Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, 2011). Grol and Grimshaw (2003) emphasize that mere dissemination of recommendations is insufficient. Implementation support is needed, especially given the rapid development of new knowledge. They also report that compliance with guidelines for acute care is generally better than for chronic care. Barriers to guideline adoption on the individual level, the care team level, and the organizational level must be understood if interventions are to succeed (Grol & Grimshaw, 2003).

On the individual level, lack of knowledge and time constraints are often identified as barriers to the adoption of CPGs in patient care (Cochrane et al., 2007; de Clercq, Blom, Korsten, & Hasman, 2004). Cabana et al. (1999) identify various factors that pose barriers to physicians' adoption of CPGs. These are classified into factors that affect knowledge, attitude, and behavior. Grimshaw, Eccles, Walker, and Thomas (2002) found that active approaches (e.g., reminders) and multifaceted interventions are more likely to affect physicians' behavior than passive dissemination of evidence. However, they emphasize that a better understanding of the influences on professional behavior and change is needed. Eccles et al. (2006) suggest that intention may be a valid proxy for behavior in the clinical setting, although the evidence is more limited than in a non-clinical setting. Kortteisto, Kaila, Komulainen, Mäntyranta, and Rissanen (2010), who explored care providers' reasons for using CPGs, found that physicians and nurses, especially in secondary care, were more positive about CPGs than other professions.

1.2.3 Clinical decision support systems

Clinical decision support (CDS) systems are a recommended active intervention strategy to facilitate the adoption of CPGs and for assistance in the delivery of safe and effective care (Institute of Medicine (U.S.) Committee on Quality of Health Care in America, 2001). Several studies have shown that reminder and alert systems can improve practitioner adherence to HIV guidelines. An early example is the study by Safran et al. (1995), which reported that computer-generated reminders and alerts increased adherence to HIV guideline recommendations. However, no effect was noted on patient outcomes. More recent studies have also shown improved adherence to CD4 testing (Were et al., 2011), as well as improved patient outcomes measured by the increase in CD4 cell counts (Robbins et al., 2012). Kitahata et al. (2003) suggest that guideline-based reminder systems may be of particular use in settings with less experienced HIV providers. Also in TB care, adherence to screening guidelines has improved with the use of CDS systems (Steele et al., 2005).

1.3 EFFECTIVENESS AND SUCCESS FACTORS OF CDS SYSTEMS

Reported effect measures are often provider performance (e.g., guideline adherence, organizational, or logistic process measures), and less frequently, patient outcome measures (e.g., changes in laboratory results, morbidity, or mortality). Latoszek-Berendsen,

Tange, van den Herik, and Hasman (2010) conclude that accurate measurement of effects on patient outcomes is difficult because of the many other factors that affect morbidity and mortality. Therefore, measuring provider adherence to guideline recommendations generated by a CDS system is the most direct indicator of effect. Mant (2001) describes two advantages of process measures compared to outcome measures in the evaluation of quality of care: 1) process measures are more sensitive to differences; and 2) process measures are easier to interpret. However, process measures are useful only if it is assumed they will produce improved outcomes.

Review studies on the effectiveness of CDS systems have shown some evidence of improved provider performance (Shea, DuMouchel, & Bahamonde, 1996; Shiffman, Liaw, Brandt, & Corb, 1999; Kawamoto, Houlihan, Balas, & Lobach, 2005; Jaspers, Smeulers, Vermeulen, & Peute, 2011; Roshanov et al., 2011; Hemens et al., 2011; Bright et al., 2012). Evidence of improved patient outcomes is inconsistent and understudied (Mollon et al., 2009).

Positive effects have been reported for CDS systems that, in particular, aim to improve treatment prescriptions/drug ordering, preventive care (e.g., vaccination), and ordering of clinical tests (Shea et al., 1996; Bright et al., 2012; Jaspers et al., 2011). These findings are consistent with a Health Technology Assessment (HTA) study by the Sahlgrenska University Hospital in Sweden (Hallin et al., 2011). This study concludes that CDS systems lead to some improvements in guideline adherence for drug prescriptions, vaccinations, and ordering of laboratory tests.

Damiani et al. (2010) reviewed the evidence on the effectiveness of CDS systems specifically intended to implement electronic guidelines. They conclude that CDS systems for electronic guidelines have a positive effect on the process of care, particularly those systems that make recommendations automatically and are integrated with the clinicians' workflow. Furthermore, they report it is a rare CDS system that makes recommendations instead of assessments. The same conclusion is applicable to affirmative feedback and the "promotion of action, rather than inaction" (Damiani et al., 2010, p. 4). Heselmans, Van de Velde, Donceel, Aertgeerts, and Ramaekers (2009) reviewed CDS systems that implemented multidimensional guidelines, which they defined as guidelines covering several steps or aspects. They found weaker support for CDS systems compared to the evidence from other studies. They suggested that this difference could be explained by the explicit exclusion of simpler reminder systems that were proven more effective in the other studies.

1.3.1 Further research needed

The evidence on the effectiveness of CDS systems as far as improving quality of care is inconclusive. For example, while the evidence for reminder systems shows they are frequently successful, the evidence for the success of active guidance systems that promote adherence to complex clinical guidelines is less clear. Moreover, Bright et al. (2012) and

Hemens et al. (2011) emphasize the insufficiency of evidence on the potential negative effects of CDS systems. More data about such effects are necessary if we are to draw reliable conclusions on the effect of CDS systems. It should also be noted that several reviews have remarked on the lack of descriptive detail about the evaluated studies, resulting in comparison difficulties (Shiffman et al., 1999; Shojania et al., 2010; Roshanov et al., 2011). Implementation details as well as user satisfaction and effect on user workflow are rarely described or analyzed (Roshanov et al., 2011). Kaplan (2001) reports that there is a preference for experimental designs to evaluate CDS systems, that focus on quantitative measures. However, other study designs (e.g., cognitive studies, usability testing, ethnography, and socio-technical analyses) are needed to identify and evaluate the factors related to the successful implementation and use of CDS systems (Kaplan, 2001).

1.4 CDS SYSTEMS TO IMPLEMENT GUIDELINES

This section examines the definition of CDS systems and different methods for encoding CPGs in a computable format, the so-called *computer-interpretable guidelines*. In this thesis, the terms *CDS* and *CDS system* are differentiated. A definition of CDS is the following:

> Clinical decision support (CDS) refers broadly to providing clinicians or patients with clinical knowledge and patient-related information, intelligently filtered, or presented at appropriate times, to enhance patient care. (Osheroff, Pifer, Teich, Sittig, & Jenders, 2005, p. x)

Hence, CDS refers to the provision of purposive, patient-specific knowledge support, regardless of the tools used. A CDS system implies the use of computing to generate patient-specific advice. A definition of CDS system is the following:

> A clinical decision support system (CDSS) is defined as software that integrates information on the characteristics of individual patients with a computerized knowledge base for the purpose of generating patient-specific assessments or recommendations designed to aid clinicians and/or patients in making clinical decisions. (Institute of Medicine (U.S.) Committee on Quality of Health Care in America, 2001, p.152)

In order to generate *patient-specific* advice, a CDS system requires access to patient data and a knowledge base. There are different approaches to modeling the knowledge base. Reasoning methods may be based on mathematical modeling, pattern recognition, statistical analysis, Bayesian modeling, decision analysis, artificial neural networks, or artificial intelligence (Musen, Shahar, & Shortliffe, 2006). However, many CDS systems

are based on simple IF-THEN-ELSE rules. Greenes (2007) states that CDS systems that perform simple calculations to generate alerts and reminders have considerable positive effect, while there is less evidence for diagnostic and treatment management support.

1.4.1 Computer-interpretable guidelines

Several methods have been proposed for the formal representation of computer-interpretable guidelines (CIGs) that can be integrated with CDS systems. By coding narrative guidelines in a computer-interpretable format, patient-specific recommendations can be generated and communicated at the point of clinical decision-making. The OpenClinical organization presents an overview of several of these methods (OpenClinical, 2002). A number of reviews and overview articles on the methods have also been published (Wang et al., 2002; Peleg et al., 2003; de Clercq et al., 2004; Mulyar, van der Aalst, & Peleg, 2007; de Clercq, Kaiser, & Hasman, 2008; Latoszek-Berendsen et al., 2010; Isern & Moreno, 2008; Peleg, 2013).

The first recognized standard for the sharing of medical knowledge in modular units — the so-called medical logic modules (MLMs) — was the Arden Syntax (Hripcsak et al., 1990). It is a rule-based language that encapsulates individual decision rules in MLMs. It was adopted as a standard by the American Society for Testing and Materials (ASTM) in 1992 and is still used in many commercial systems (OpenClinical, 2002). While the Arden Syntax has been used to encode clinical practice guidelines, it has several shortcomings that make it unsuitable for representing CIGs. For example, the Arden Syntax does not allow shareable implementations of guidelines, its syntax rules are modular with no control structure for modeling processes that evolve over time, and the data model is too simplistic for current standards (Sonnenberg & Hagerty, 2006).

To address the shortcomings of the Arden Syntax, in the 1990s several research groups developed new guideline representation models that could represent multi-step guidelines (Elkin et al., 2000). This research resulted in the now common Task Network Models (TNMs), which are defined as a "hierarchical decomposition of guidelines into networks of component tasks that unfold over time" (Peleg et al., 2003). Representations of actions and decisions are core components of such models (Wang et al., 2002). A control-flow language specifies the relations (e.g., sequential links and branching) between components. An expression language is needed to describe eligibility and decision criteria. Finally, a guideline execution engine is needed to generate patient-specific recommendations (Latoszek-Berendsen et al., 2010).

Two TNM formalisms that have been used in CDS systems for HIV care are EON (Musen, Tu, Das, & Shahar, 1996) and PRO*forma* (Fox et al., 1997). The EON formalism was used to model the T-HELPER system for AIDS and HIV-related care (Musen, Carlson, Fagan, Deresinski, & Shortliffe, 1992). The system consisted of an electronic patient record, a therapy-planning component, an eligibility assessment component, and a clinical trial

protocol knowledge base (Musen et al., 2006, p. 599). The T-HELPER system would indicate if a patient was eligible for a clinical trial protocol. If the patient was enrolled, the system would recommend the needed therapy.

The PRO*forma* formalism was used in the RetroGram system to provide antiretroviral therapy advice based on HIV–1 genotype information (Fox, Patkar, & Thomson, 2006). A randomized controlled trial showed that genotypic testing with interpretation support by the RetroGram system led to improved virological outcomes (Tural et al., 2002). However, the relative contribution of this CDS system to the improved outcomes could not be determined.

In an effort to facilitate standardization, six predominant formalisms (Asbru, EON, GLIF, GUIDE, PRODIGY, and PRO*forma*) were systematically compared (Peleg et al., 2003). The structural organization of guidelines was similar in most of the formalisms. However, the computational models used in these formalisms varied considerably, and the different models varied in scope. The comparison study concluded that while it was not feasible to set a standard, individual components could be standardized and shared. The focus on model standardization has shifted to sharing of CIG knowledge, which is still an important research topic (Peleg, 2013).

Only a few CIG methods have been implemented in clinical settings (Isern & Moreno, 2008; Gooch & Roudsari, 2011). The TNM-based formalisms have been criticized for their lack of flexibility (Grando, Glasspool, & Boxwala, 2012). Shalom et al. (2008) noted that CIG methods are typically demonstrated using disease guidelines with a well-defined clinical pathway. The clinical trial protocols in the T-HELPER system are an example of this. However, in some settings, the rigid workflow structuring and task sequencing may hinder the work of care providers (Patkar & Fox, 2008).

1.5 INTERACTION DESIGN OF CDS SYSTEMS

Interaction design, as this term is used here, refers to the interaction between the user and the CDS system. Musen et al. (2006) describe two characteristics that relate to the interaction design: 1) the mode used to offer the advice; and 2) the communication style. CDS systems can be described as *active* or *passive*, depending on the way in which advice is offered. The communication style can be either *critiquing* or *consulting*.

1.5.1 Mode by which advice is offered (active or passive)

A CDS system may offer advice in an *active* or *passive* mode (Musen et al., 2006). An active system, which is automatically initiated by events or time triggers, does not require any user effort (Greenes, 2007). Alert and reminder systems are examples of active systems that may help prevent unintentional medical errors (Tamblyn et al., 2008). A disadvantage of such systems is that they may also cause workflow disruptions and alert

fatigue. In order to avoid alert fatigue, thresholds for alerts and reminders should be calibrated (Bates et al., 2003). A passive system, on the other hand, is triggered by the user. Its advantage is that the user, rather than the system, decides on the advice and its implementation. The disadvantage is that, before actively initiating the system, the user must be aware of the need for support.

Automatic (i.e., active) CDS systems have been shown to be more effective than on-demand (i.e., passive) CDS systems (van Wyk et al., 2008). However, these findings are not consistent. Reminders may not always lead to expected improvement of practitioner performance (Kortteisto et al., 2014). In their review study, Hemens et al. (2011) found no association between automatic provision of decision support and CDS system success.

1.5.2 Communication style (critiquing or consulting)

A CDS system may use a *critiquing* or a *consulting* communication style (Musen et al., 2006). The critiquing style agrees with provider decisions or suggests alternative decisions. In simple patient cases, this style is effective in issuing alerts and reminders. However, there is also a need for CDS in more complex cases, such as patients with multiple medications or chronic conditions (Sittig, Krall, Dykstra, Russell, & Chin, 2006; Bright et al., 2012). In such cases, the consulting style may be more useful as a support for complex decision-making because it is more specific and more flexible (Bouaud, Séroussi, Falcoff, & Venot, 2006). The consulting style generates advice on, for example, diagnoses or treatments that are based on patient-specific characteristics, and, in some cases, other user data (Musen et al., 2006). The critiquing style has had greater effect on patient outcomes than the consulting style (Sintchenko, Magrabi, & Tipper, 2007).

1.6 ACCEPTANCE AND USE OF CDS SYSTEMS

Kortteisto, Komulainen, Mäkelä, Kunnamo, and Kaila (2012) describe the perceived usefulness of CDS systems as a decisive factor affecting system use. Kilsdonk, Peute, Knijnenburg, and Jaspers (2011) have found that the most frequently reported influential factors on system use among physicians are their expectations and beliefs about CDS systems. Physicians are more willing to use such systems if they can use and control them efficiently.

Kushniruk (2001) has found that physicians' reasoning processes and patterns, when making diagnoses or prescribing treatment plans, may be greatly influenced by the way in which information is organized and presented in computer interfaces. Therefore, different strategies of information processing and decision-making should be considered both in the design and in the evaluation of computer-based systems.

The *five rights model* states that CDS systems should convey the following: 1) the right *information*, 2) to the right *person*, 3) in the right intervention *format*, 4) through the right *channel*, 5) at the right time in the *workflow* (R. Campbell, 2013, original emphasis).

Specifically, researchers emphasize that CDS systems should require minimal user effort, should be delivered at the time of decision-making, and should be integrated with the user's workflow (Kawamoto et al., 2005; Bates et al., 2003; James, 2002).

1.6.1 User-centered design

Studies have shown that the design of CDS systems using a user-centered approach may increase the usability of CPGs (Verhoeven, Steehouder, Hendrix, & Van Gemert-Pijnen, 2010; Kilsdonk, Peute, Riezebos, Kremer, & Jaspers, 2013). J. Iivari and N. Iivari (2011) describe user-centeredness as a composition of user focus, work-centeredness, user involvement, and system personalization. According to Gulliksen et al. (2003), user participation is a key criterion for successful IT development. They describe 12 key principles of user-centered system design that cover the analysis, design, evaluation, construction and implementation phases. Users should participate in these phases that take into account user needs, goals, and work domains. Simple design representations, such as mockups and prototypes, should be developed in an iterative process to visualize and evaluate the design ideas. All phases should focus on usability, which is defined as "the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use" (International Organization for Standardization, 2010). Hence, the usability of an artifact depends on the experience of individual users in a context.

2 AIM AND OBJECTIVES

The aim of this thesis was to explore how a clinical decision support (CDS) system could be designed to support the adoption of evidence-based guidelines in the treatment of HIV-related TB. The thesis covers three phases: (1) contextual analysis, (2) design, and (3) evaluation. The specific objectives of the four studies in this thesis are stated below:

1. **Contextual analysis**

    - To explore the challenges faced by nurses and physicians in the treatment of HIV-related TB, with a major focus on identifying opportunities for information and communication technology. (Study I)
    - To describe socio-demographic and clinical characteristics of patients with HIV-related TB in a Swedish cohort, and to identify factors associated with success in anti-TB treatment and with adverse reactions to anti-TB treatment. (Study II)

2. **Design**

    - To design a CDS prototype to support care providers in the adoption of guidelines for HIV-related TB treatment. The CDS prototype includes 1) a knowledge base model of drug therapy guidelines, and 2) a graphic user interface for care providers. (Study III)

3. **Evaluation**

    - To evaluate the conceptual design of a CDS prototype for treatment guidelines for HIV-related TB. (Study IV)

3 OVERVIEW OF THE THESIS

The four studies in this thesis deal with different phases of a user-centered approach to designing a CDS prototype that aims to promote evidence-based care in the treatment of HIV-related TB. A graphic overview of the individual studies is presented in Figure 3.1. The first phase, consisting of two studies, is a contextual analysis of the setting: Study I explores the challenges and needs experienced by care providers with different levels of expertise and experience in the treatment of HIV-related TB; Study II describes socio-demographic and clinical characteristics of patients in this setting and analyzes patient outcome data. The knowledge acquired in these two studies was used to inform the design and evaluation phases, which also consist of two studies: Study III proposes a CDS framework for drug therapy recommendations that is applied to HIV-related TB guidelines by designing a CDS prototype; Study IV formatively evaluates the CDS prototype by exploring care providers' perceptions of its conceptual design.

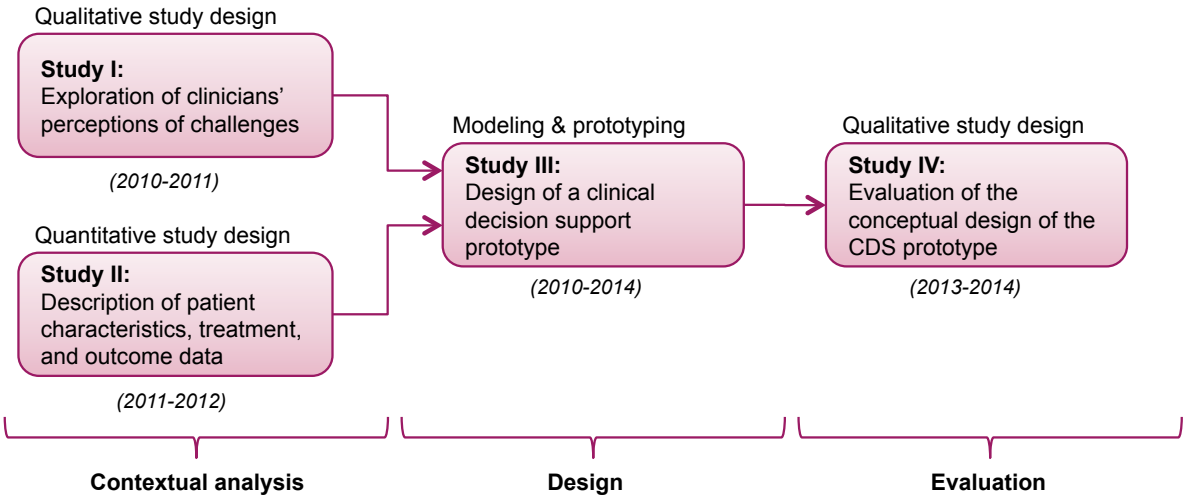

FIGURE 3.1: Overview of the thesis. The square boxes represent the individual studies in the thesis. The time periods of the studies are indicated in parentheses.

4 METHODS

A multi-strategy design was used to explore challenges of HIV-related TB treatment from a qualitative perspective (Study I) and from a quantitative perspective (Study II), and to design and formatively evaluate a CDS framework and prototype (Studies III and IV). This chapter is structured as follows: section 4.1 describes the study setting; section 4.2 presents an overview of the research participants; section 4.3 and section 4.4 describe the overall study design, data collection, and analytical methods used in the individual studies; section 4.5 describes ethical considerations. A summary overview of the details of the individual studies is presented in Table 4.1.

4.1 SETTING

The HIV outpatient clinic at the Karolinska University Hospital, Stockholm, was chosen as the setting for this thesis. The clinic's size was one reason for choosing this setting. It is the largest HIV outpatient clinic in Sweden (Svedhem, 2013). At the time of writing, the clinic cares for about 1,800 of the 6,200 HIV-infected patients in Sweden. The staff consists of physicians, nurses, counselors, and secretaries. Staff and patient numbers for 2010 and 2013 (years of data collection for Studies I and IV) are presented in Table 4.2. A second reason for choosing this setting was that one member of the research team is employed at the hospital as a Senior Consultant in Infectious Diseases. This placement gave the team full access to the research setting.

TABLE 4.2: Patients and staff at the HIV outpatient clinic.

	Year	
	2010	2013
Approx. no of patients	1600	1800
No. of physicians	16	13
No. of nurses	13	11

Karolinska University Hospital is the largest of seven university hospitals in the six medical care regions in Sweden (Anell, Glenngård, & Merkur, 2012). The hospital is owned by the Stockholm County Council and was established by a merger between the Karolinska Hospital and the Huddinge University Hospital in 2004 (Karolinska University Hospital, 2005). There are two major centers: Karolinska Solna in the north of Stockholm, and Karolinska Huddinge in the south of Stockholm. The Infectious Diseases Department has TB wards at both centers and an HIV outpatient clinic at Karolinska Huddinge.

There are 290 municipalities and 20 county councils in Sweden (Swedish Association of Local Authorities and Regions, 2009). Stockholm County Council is the largest council, with a population of nearly 2.2 million inhabitants (Stockholm County Council, 2014).

TABLE 4.1: Research design and methods for the four studies in the thesis.

Study	Research design	Focus	Data collection method	Data sources	Analysis/design method
I	Cognitive task analysis	Care provider perceptions	Observations at the HIV clinic; task diagram interviews (2 physicians, 2 nurses); critical decision method inspired interviews (4 physicians, 5 nurses)	Interview transcripts	Inductive thematic analysis
II	Retrospective study	Patient characteristics, treatment, and outcomes	Review of medical records and the InfCare HIV quality registry of patients treated for HIV/TB coinfection in Stockholm County Council (1987–2010)	*Nominal variables:* Sex, geographic origin, route of HIV transmission, diagnostic findings and clinical manifestation of TB, comorbid conditions at TB diagnosis (other ADIs, chronic hepatitis B/C), antiretroviral and anti-TB treatment, anti-TB drug resistance, ADRs, anti-TB treatment outcome, TB recurrence *Continuous variables:* Age, CD4 cell counts and HIV RNA viral load (at or within 6 months of TB diagnosis) *Dates:* HIV diagnosis, cART initiation, TB diagnosis, completion of anti-TB treatment, death	*Descriptive statistics:* percentages for nominal variables, median and interquartile range (IQR) for continuous variables *Group comparisons:* Chi-square test or where appropriate Fisher's exact test for nominal variables, Mann-Whitney *U*-test for continuous variables when the distribution deviated from normality *Multiple logistic regression*: Odds ratios (OR) with 95% confidence intervals (CI)
III	Design study	EviTMA (evidence-based Treatment, Monitoring, and Assessment) CDS framework	Analysis of clinical guidelines and protocols; prototype discussion meetings (2 physicians, 2 nurses)	Clinical guidelines and protocols; feedback notes	Graphic user interface prototyping, knowledge base modeling using UML
IV	Evaluation study	Care provider perceptions	Focus groups (4 physicians, 10 nurses)	Focus group transcripts	Step 1: deductive thematic analysis based on UTAUT Step 2: inductive thematic analysis within UTAUT constructs

Abbreviations: ADI, AIDS-defining illness. ADR, adverse drug reaction. cART, combined antiretroviral treatment. CDS, clinical decision support. UML, unified modeling language. UTAUT, unified theory of acceptance and use of technology.

The county councils are responsible for the funding and provision of health care (Anell et al., 2012). The Swedish National Board of Health and Welfare provides national guidelines for the allocation of resources in Health and Medical Care and Social Care (National Board of Health and Welfare, 2014a).

All cases of suspected or confirmed HIV or TB disease must be reported to The Public Health Agency of Sweden and The County Medical Officer. These cases are also subject to mandatory contact tracing (National Board of Health and Welfare, 2014b). The Swedish Communicable Diseases Act regulates this reporting (SFS 2004:168, 2004). The Act also requires that such treatment be provided at no charge to patients. Because some of the drugs are very expensive, HIV/AIDS treatment is covered by a system of reallocation of funds among the county councils (Anell et al., 2012).

4.1.1 Organization of care at the HIV outpatient clinic

All patients at the HIV outpatient clinic have a designated care team that consists of a physician, a nurse, and a counselor. The planning of care is the shared responsibility of the care team. Physicians are medically responsible for patients, and nurses are responsible for monitoring treatment and administering drugs. Counselors support and motivate patients as well as conduct the HIV contact tracing. As the counselors have no responsibility for the drug therapy, this thesis does not examine their role in patient care. The focus of this thesis is specifically on the tasks performed by physicians and nurses in the treatment of patients with HIV-related TB.

4.1.1.1 Treatment of HIV-related TB

The treatment of HIV-related TB is the responsibility of the HIV outpatient clinic. The treatment and the tasks performed by physicians and nurses are illustrated in Figure 4.1.

Diagnosis Some patients may have severe immunosuppression when they are diagnosed with TB. This is typically the case with patients whose HIV-infection has not been previously diagnosed. It is routine to offer to test patients for HIV when TB is suspected. Therefore, some patients are simultaneously faced with two severe diagnoses, both with complicated drug regimens. For patients who are on an antiretroviral drug regimen when TB is diagnosed, anti-TB drugs are administered taking into consideration the possible drug-drug interactions. For patients who are not in antiretroviral therapy when they are diagnosed with TB, treatment is initiated with only anti-TB drugs for the first couple of weeks. Depending on the patient's immune status, antiretroviral therapy may be introduced after 2 to 8 weeks.

Treatment and monitoring If patients are very ill or if there is a risk of contamination, anti-TB treatment is initiated at the inpatient clinic. After discharge, patients continue

their treatment at the HIV outpatient clinic. The anti-TB treatment lasts for at least six months (a 2-month initiation phase followed by a 4-month continuation phase).

During the initiation phase of two months, patients see nurses for weekly or bi-weekly visits where their drugs are administered and monitored. Physician visits are scheduled after four weeks and after two months. During the continuation phase of about four months, patients have monthly follow-up visits with nurses. Physician appointments are less frequent (about bi-monthly); the recommended schedule for both nurse and physician appointments may vary depending on patient needs.

Physicians who have specialized in TB treatment are only involved if their assistance is requested. However, at the time of this research, the HIV outpatient clinic did not have access to all the monitoring equipment that was needed for TB follow-up. Therefore, nurses at the TB outpatient clinic assisted with ophthalmology controls. TB contact tracing was also performed at the TB outpatient clinic.

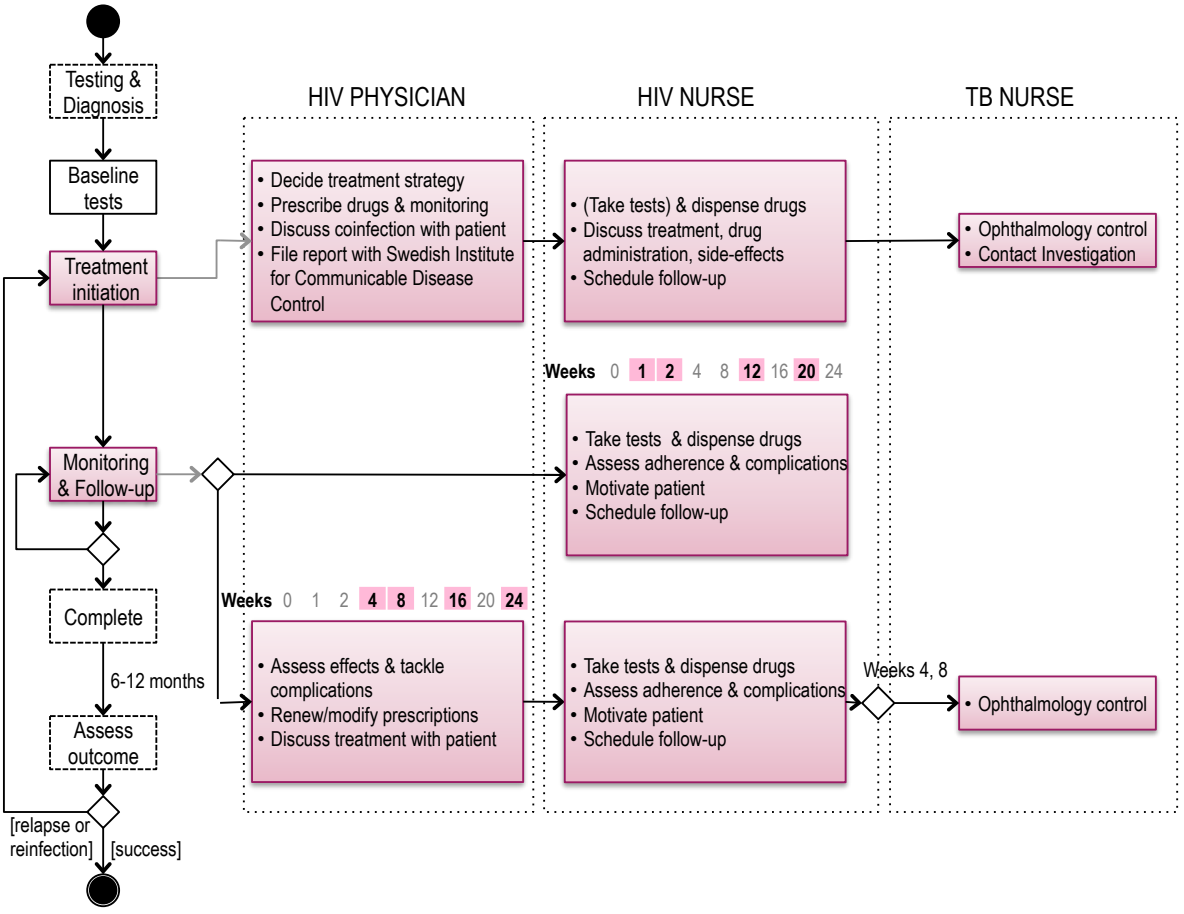

FIGURE 4.1: The treatment process of HIV-related TB disease. The vertically oriented process on the left illustrates the overall tuberculosis treatment process from start to end. The three horizontally oriented processes represent the patient's path at treatment initiation and monitoring & follow-up appointments. The week numbers indicate when the care visits are planned (treatment initiation = week 0). The tasks of physicians and nurses are outlined in the shaded boxes.

Follow-up Treatment success is evaluated six to twelve months after treatment completion.

4.1.2 Swedish national guidelines

In 2009, a guidance document was published with the stated purpose of increasing knowledge about TB and providing uniform guidelines for treatment and care (National Board of Health and Welfare, 2009).

National recommendations for antiretroviral therapy of HIV-infection have been published and revised regularly since 2002 by the Swedish Reference Group for Antiviral Therapy (RAV) and the Medical Products Agency (Public Health Agency of Sweden, 2014). The most recently revised version was published in 2013 (Referensgruppen för antiviral terapi, 2014).

4.1.3 Technical context

Sweden is a leading country in its use of information and communication technology (ICT) in healthcare. All counties in Sweden use an EHR system for the clinical documentation of care (Jerlvall & Pehrsson, 2013). TakeCare (CGM, CompuGroup Medical) is the most widely used EHR system in Sweden, with about 37,000 users (Profdoc Care AB, 2014b). The Karolinska University Hospital has used TakeCare since the merger in 2004 and in 2008 it was decided to implement it throughout Stockholm County Council (Profdoc Care AB, 2014a).

InfCare HIV is a national quality registry for all Swedish HIV clinics. The registry is also used as a tool for CDS and (tele-)consultations at the point of care (Rosén, 2010). The CDS module graphically visualizes clinical data from several sources. Individual patients' drug therapy over time, HIV viral load, and CD4 cell counts are displayed in one graph, giving care providers a good overview of the progress of patient treatment. Additionally, the graph displays HIV-resistance and drug concentrations (Sönnerborg, 2007). The graph is used for (tele-)consultations with other care providers, for consultation meetings, and for discussions with patients. InfCare HIV can be accessed from the EHR system, but there is no integration of clinical data between the two systems. The laboratory parameters for the graph display are accessed directly from the clinical laboratory. However, each patient's drug therapy information must be registered manually.

4.2 OVERVIEW OF THE STUDY PARTICIPANTS

Physicians and nurses were selected for participation in Studies I, III, and IV because they share the main responsibility in the HIV/TB drug therapy. Purposeful sampling was used to identify participants for the studies (Patton, 2002). Most participants practiced at the HIV outpatient clinic where patients with HIV-related TB are treated. However,

most physicians did not practice full-time at the HIV outpatient clinic. Furthermore, some TB specialists were also involved because of their medical expertise. Altogether, 13 nurses and 9 physicians participated in one or more of the four studies in this thesis, as illustrated in Table 4.3.

TABLE 4.3: Study participants in Studies I,III, and IV.

			Participation		
ID	Role	Infectious Diseases Unit	Study I	Study III	Study IV
N01	RN	HIV outpatient clinic	x	x[a]	x
N02	RN	HIV outpatient clinic	x[a]	x[a]	x
N03	RN	HIV outpatient clinic	x	x	x
N04	RN	HIV outpatient clinic	x		x
N05	RN	HIV outpatient clinic	x		x
N06	RN	TB clinic	x		
N07	RN	TB clinic	x		
N08	RN	HIV outpatient clinic	x		
N09	RN	HIV outpatient clinic		x	x
N10	RN	HIV outpatient clinic			x
N11	RN	HIV outpatient clinic			x
N12	RN[c]	HIV outpatient clinic			x
N13	LPN[c]	HIV outpatient clinic			x
P01	MD	HIV outpatient clinic	x	x	
P02	MD	TB clinic	x		x
P03	MD	TB clinic	x		x
P04	MD[b]	HIV outpatient clinic	x		
P05	MD[b]	HIV outpatient clinic	x		
P06	MD	HIV outpatient clinic	x		
P07	MD	HIV outpatient clinic		x	
P08	MD	HIV outpatient clinic			x
P09	MD	HIV outpatient clinic			x

[a] Informal participation. [b] Resident. [c] Research profile. Abbreviations: RN, registered nurse. MD, medical doctor. LPN, licensed practical nurse.

4.3 CONTEXTUAL ANALYSIS

Studies I and II identify and describe the challenges in HIV/TB care where CDS might be useful.

4.3.1 Study I - Qualitative contextual analysis

4.3.1.1 Study design

A qualitative research approach based on cognitive task analysis (CTA) was used to explore the challenges that care providers face in managing HIV-related TB. Qualitative research methods are appropriate when the research purpose is to explore "people's experiences, perceptions, opinions, feelings, and knowledge" (Patton, 2002, p. 4). CTA is

a specific qualitative approach that can be used to explore and explain the mental processes that are involved in performing a task, such as clinical decision-making among care providers in the studied context (Klein & Militello, 2001). Multiple data collection methods are often used in combination (Crandall, Klein, & Hoffman, 2006, p. 15). In this study, observations and interviews were used to identify challenging tasks and to explore the perceptions of care providers related to their decision-making and work routines.

Field observations were made at the HIV outpatient clinic so the author could acquaint herself with the clinical setting and the care providers' workflow. Observations allow the researcher to gain a deeper insight into a research context, which is essential for a holistic perspective (Patton, 2002). The insights acquired by observations can support the analysis of other data sources, such as interviews (Patton, 2002).

The interviews, which were conducted with physicians and nurses, allowed the author to expand on her observations of external behavior and to explore more deeply the interviewees' perceived challenges (Patton, 2002, p.306). Two different semi-structured interview techniques were selected: the *task diagram interview* and the *critical decision method* (CDM).

The task diagram interview is a technique that was developed for Applied Cognitive Task Analysis (ACTA), which is a streamlined method of CTA (Militello & Hutton, 1998). The purpose of this type of interview, which is conducted with subject matter experts, is to gain a surface-level overview of a task and to identify elements that are cognitively challenging. The findings are captured in a task diagram that guides future in-depth interviews. In this study, task diagrams of clinical tasks in the treatment process of HIV-related TB were mapped. CDM-inspired interviews were then conducted that further explored the challenges in the identified tasks.

The CDM is an in-depth interview technique that is suitable for gathering "information about cognitive functions such as decision-making and planning and sensemaking within a specific challenging incident" (Crandall et al., 2006, p. 73). The interview concerns a retrospective narrative of a non-routine event in which the interviewee, who is an expert in the studied field, has played a key role. The CDM is conducted in four so-called *sweeps* (Crandall et al., 2006, p. 73ff): in the first sweep, an incident is selected; in the second sweep, key events are plotted on a time line; in the third sweep, probes are used to explore the cognitive functions and processes of key events; and in the fourth sweep, "what if" questions are asked to identify expert-novice differences. In this study, the CDM interview was used to explore care providers' perceptions of their general challenges encountered in treatment planning and decision-making. The approach is referred to as CDM-*inspired* because the narrow focus on single incidents gradually shifted to a broader focus on experienced challenges in general.

4.3.1.2 Data collection and analysis

Sampling strategy Participants were selected based on their expertise (HIV or TB) and experience (e.g., specialist/resident). Variations in these dimensions were sought. Snowball sampling was used to identify additional participants (Patton, 2002). Subject matter experts for the task diagram interview were identified for the two specialties (HIV and TB) and the two professional roles (physician and nurse) – i.e., four participants in total. In the CDM-inspired interviews, the majority of the participants were selected from the HIV outpatient clinic where patients with HIV-related TB are treated. Four physicians (1 HIV specialist, 1 TB specialist, and 2 residents at the HIV outpatient clinic) and five nurses (4 HIV nurses, and 1 TB research nurse) participated (Table 4.3).

Data collection During one week, on-site observations at the HIV outpatient clinic were made, and informal discussions with the clinic's physicians, nurses, and counselors were conducted. The author's purpose with these observations and discussions was to become acquainted with the clinical setting and the work routines. The aim was to learn the following: how the organizational and technical systems work; how care providers interact and collaborate; which documents and information resources are used; who the potential subject matter experts for subsequent interviews are; which tasks seem to require tacit knowledge; and which tasks seem to be cognitively challenging. Physicians and nurses were observed before, during, and after patient encounters. Also, one of the weekly consultation meetings among the physicians was observed.

The author, who conducted the interviews, used an interview guide to make sure all relevant themes were addressed (Appendix Study I). Separate interview guides were used for the task diagram interviews and the CDM-inspired interviews. In the former, care providers were asked to reflect on the major steps they took prior to, during, and after patient encounters. They were also asked to identify which tasks were most cognitively challenging. Task diagrams were developed as mind-maps. All interviewees in the CDM-inspired interviews were shown a task diagram and were asked to describe an event in which they had to make a decision involving one or more of the previously identified challenging tasks. All interviews were audio recorded and lasted for approximately 30 minutes to 2 hours. The CDM-inspired interviews were generally longer.

Data analysis Hand-written notes from the observations and the informal discussions described the treatment process of HIV-related TB. The interviews, which were conducted in Swedish, were transcribed verbatim and then analyzed using inductive thematic analysis (Braun & Clarke, 2006). The individual steps of the analysis are detailed in Figure 4.2. The qualitative data analysis program Nvivo (Version 9; QSR International, Doncaster, VIC, Australia) was used to code and categorize the data. Although the interview transcripts were in Swedish, English code and category labels were used to facilitate the reporting of findings. Illustrative interviewee comments were translated into English and presented as quotes.

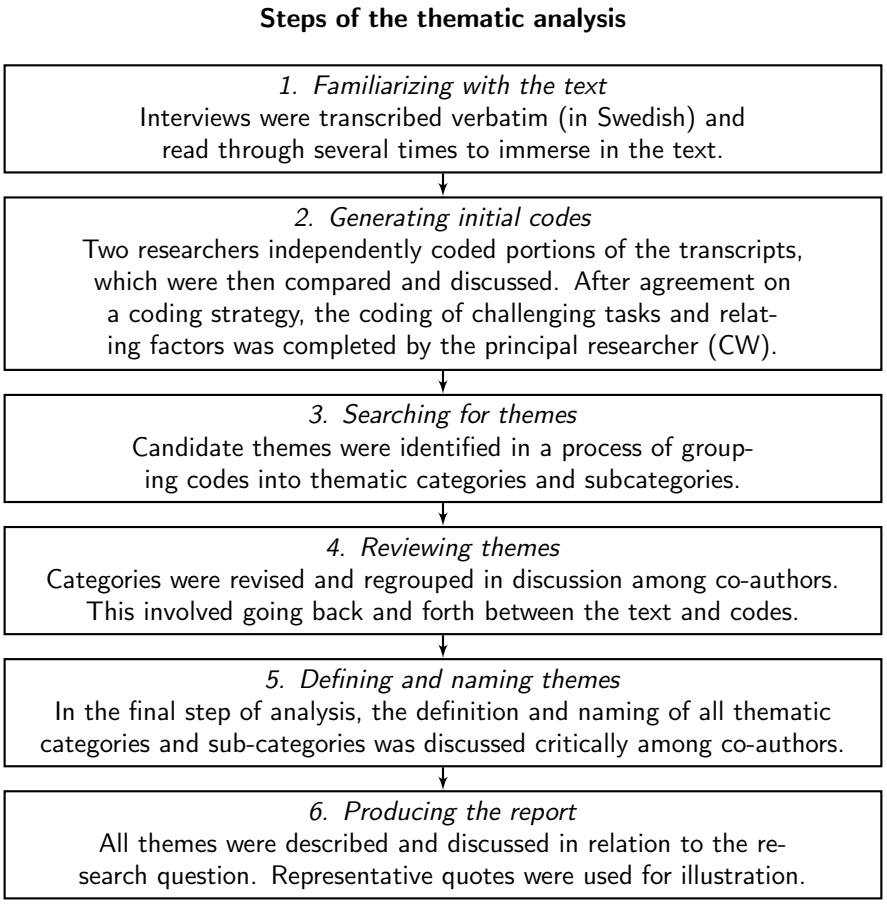

FIGURE 4.2: Individual steps of the thematic analysis of interview transcripts in Study I, based on the process described by Braun and Clarke (2006).

4.3.2 Study II - Quantitative contextual analysis

4.3.2.1 Study design

This study used a quantitative retrospective design for the data from 1987 to 2010 to describe the context of HIV-related TB care. Because a highly effective combination therapy for HIV (cART) was introduced in 1996, the study population was stratified into two groups, hereafter referred to as cohorts: the *early cohort* (1987 to 1995, before the introduction of cART) and the *late cohort* (1996 to 2010, after the introduction of cART). Sociodemographic and clinical characteristics of patients were described and compared for the two cohorts. In the late cohort, cART was evaluated as a possible predictor of anti-TB treatment success and of adverse reactions. Anti-TB treatment success was classified as successful if patients completed treatment without any registered TB recurrence within the follow-up period until the end of 2011. Adverse reactions were defined as severe noxious or unintended responses to the anti-TB treatment that resulted in a (temporary) discontinuation or modification of the treatment.

4.3.2.2 Data collection and analysis

Inclusion criteria The following inclusion criteria were specified: adult patients (≥18 years at the time of the TB diagnosis), HIV-infection and TB disease in the study period, diagnosis and treatment in the Stockholm County Council. Of the 189 identified patients, 62 patients were excluded as explained in Figure 4.3. Thus, the total study population consisted of 127 patients: 26 in the early cohort and 101 in the late cohort.

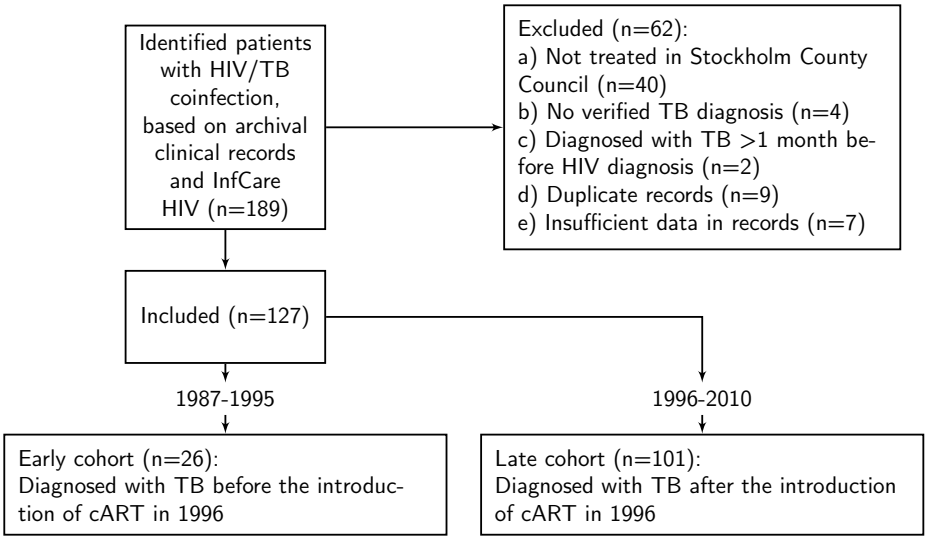

FIGURE 4.3: Study population and stratification, Study II.

Data collection Primary data for HIV-infected patients who were treated for TB disease in the Stockholm County Council from January 1987 to December 2010 were collected from medical records. Secondary data were collected from the InfCare HIV quality registry and archival records. Data were first recorded manually on paper records. Thereafter, the data were transferred to an electronic database management system.

Statistical analysis Descriptive statistics were used to analyze socio-demographic and clinical data. The median and the interquartile range (IQR) was presented for numeric variables. Percentages were presented for categorical variables. Comparisons between the two cohorts were made using the Mann-Whitney U-test for continuous variables when the distribution deviated from normality. A chi-square test was also used, or, where appropriate, Fisher's exact test for categorical variables was used. The level of statistical significance was specified at 5%.

Multivariate logistic regression analyses were performed in the late cohort to evaluate the influence of cART on anti-TB treatment success and adverse reactions. Reference values for all variables were coded as 0. In the analysis of treatment success, the predictor variable cART was coded as a dichotomous variable (cART=1, no cART=0). The following control variables were included in the analysis: sex (female=1, male=0), age in

years (≤37=1, >37=0; 37 was the median age in the cohort), and CD4 counts (cells/μL) at the time of TB diagnosis (>200=1, ≤200=0). In the analysis of adverse reactions, the predictor variable cART was coded as a three-leveled variable (before TB-diagnosis=1, after TB-diagnosis=2, no cART=0). The same control variables were included, but CD4 counts (cells/μL) were coded the opposite way (≤200=1, >200=0). The reason was that poor immune status (CD4 count ≤200 cells/μL) was expected to have a possible negative association with treatment success, and a possible positive association with adverse reactions. Univariate logistic regression analyses were performed to determine the crude association of all independent (predictor) variables with the dependent (outcome) variables. Multicollinearity between independent variables was determined based on the variance inflation factor (VIF). The threshold for multicollinearity was set at VIF >4. Goodness-of-fit was examined using the Hosmer and Lemeshow test.

4.4 DESIGN AND FORMATIVE EVALUATION OF A CDS PROTOTYPE

Studies III and IV address the design and formative evaluation of a CDS prototype that can be used to deal with some of the challenges that were identified in the contextual analysis.

4.4.1 The eviTMA framework

Clinical practice guidelines (CPGs) guide physicians in their decision-making for treatment and follow-up. Additional knowledge is needed to assess the potential benefits and harms of different options: knowledge about indications and contra-indications of drugs, interactions between drugs, and (known) intended and unintended effects of drugs.

Because the purpose of a drug therapy is to improve or maintain a health condition, the patient's response to treatment must be monitored continuously to assess the progress that will inform decisions about future steps (e.g., whether to continue, modify, or stop a drug therapy). This thesis proposes the eviTMA (evidence-based Treatment, Monitoring, and Assessment) framework to model evidence-based drug therapy recommendations. The choice of treatment informs monitoring activities. Monitoring results enable assessment of treatment progress. Assessment then informs future treatment decisions. A conceptual model of the eviTMA framework is presented as a directed cyclical graph in Figure 4.4.

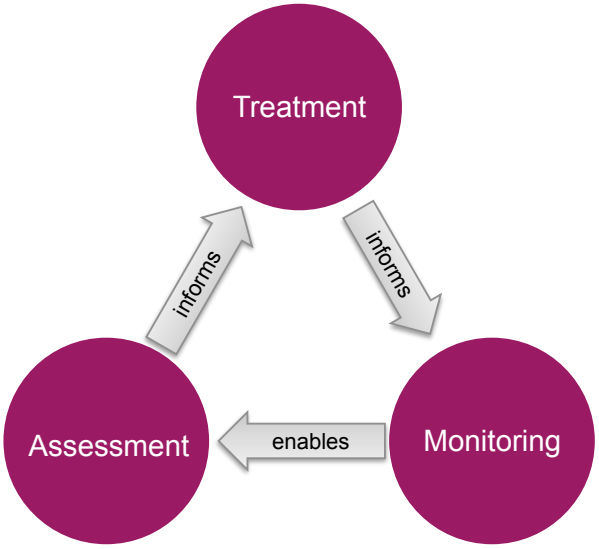

FIGURE 4.4: Conceptual model of the eviTMA (evidence-based Treatment, Monitoring, and Assessment) framework. The arrows between the circles represent relationships. The choice of treatment informs monitoring activities. Monitoring results enable assessment of treatment progress. Assessments then inform future treatment decisions.

4.4.2 Study III - Design

4.4.2.1 Study design

A user-centered approach was used to design a CDS prototype for HIV-related TB drug therapy recommendations, based on the eviTMA framework. Norman and Draper (1986, p. 61), who coined the term *user-centred design*, emphasized that "[t]he needs of the users should dominate the design of the interface, and the needs of the interface should dominate the design of the rest of the system". In this study, prototyping and the Unified Modeling Language (UML) were used in combination.

Prototyping was used to design the graphic user interface (GUI), or front-end, of the CDS prototype (visible to end-users). It is a recommended technique that creates a common understanding between users (e.g., physicians and nurses) and designers (Gulliksen et al., 2003). In this study, the design was informed by the challenges identified in the contextual analysis (Studies I and II). It was formatively improved by discussing evolving versions of the GUI prototype with the care providers.

The UML was used to design and describe a knowledge base model of drug therapy guidelines, or back-end, of the CDS prototype (not visible to end-users). The UML is a standardized pictorial (symbolic) language that is used within the field of systems development to formalize systems analysis and design by models (Kimmel, 2005). A system's structure and interaction with users can be represented by different types of diagrams. Class diagrams are diagram types that can be used to describe the static structure of a

system in terms of objects and their attributes, operations, and relationships (Bruegge & Dutoit, 2009, p. 77). In this study, the UML class diagram was used to describe a knowledge base model of drug therapy guidelines for HIV-related TB treatment.

4.4.2.2 Design procedure

Sampling strategy Study participants – some of whom had previously been involved in the project and some who had not – were invited to provide feedback on evolving versions of the GUI prototype. Two physicians and two nurses participated. One physician and one nurse had participated previously; the others were new to the project (Table 4.3).

Prototyping The GUI prototype was created using Microsoft® PowerPoint®, which is a widely available and much used tool. While the tool is not specifically intended for GUI design, its functionalities were acceptable for the purpose of this study.

The research team developed initial design sketches. The team discussed these sketches informally with some care providers at the HIV outpatient clinic (see *informal participation*, Table 4.3). When the GUI prototype achieved a sufficient level of functionality and content specification, the study participants were invited to offer feedback on the design in formal one-to-one discussion meetings. The author presented the prototype using a fictitious patient case scenario and a discussion guide (Appendix Study III). The discussion guide was designed to elicit the participants' views on the functionality and content of the prototype, as well as their ideas on on how the envisioned CDS system could be integrated with the clinical workflow. The author took notes during the discussion and compiled summaries that were sent to the study participants individually for their review.

Knowledge base modeling using UML The knowledge sources used consisted of CPGs issued by national and international authorities (Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents, 2013; Referensgruppen för antiviral terapi, 2014; National Board of Health and Welfare, 2009), clinical protocols at the HIV outpatient clinic, and the summary of product characteristics (SPCs) of anti-TB drugs as described in FASS (The Swedish Medicines Information Engine) ("FASS," 2014). The documents were examined for treatment, monitoring, and assessment recommendations. Concepts and relationships were extracted and modeled in a UML class diagram, which represented the knowledge base model. The class diagram was iteratively refined during the development process.

4.4.3 Study IV - Formative evaluation

4.4.3.1 Study design

A qualitative approach based on user-centered evaluation was used to formatively evaluate a functional version of the CDS prototype proposed in Study III. User-centered evaluation (UCE) can verify the quality of a product, detect problems, and support decisions (van Velsen, van der Geest, Klaassen, & Steehouder, 2008; De Jong & Schellens, 1997). In this study, the purpose was mainly to gain knowledge about prospective end-users' perceptions of the conceptual design of the CDS prototype and to detect usability concerns that might help to improve its design and inform future implementation. The CDS prototype was demonstrated to care providers and evaluated using focus groups. The Unified Theory of Acceptance and Use of Technology (UTAUT) (Venkatesh, Morris, Davis, & Davis, 2003) was applied as an analytical framework.

Focus groups were held with the physicians and nurses at the HIV outpatient clinic. A focus group is "an open-ended group discussion which the researcher guides, typically extending over at least an hour, possibly two or more" (Robson, 2011, p. 294). In user-centered evaluation studies, focus groups are suitable for acquiring an understanding of the attitudes, behaviors, and intentions of users (van Velsen et al., 2008). In this study, the conceptual design and usability of the demonstrated CDS prototype were the foci of the evaluation.

The UTAUT was applied as an analytical framework because it is an evaluated model that has been shown to explain 70% of the variance in the intention with using technology (Venkatesh et al., 2003). According to the UTAUT, intentional behavior in using technology is determined by *performance expectancy*, *effort expectancy*, and *social influence*. The intentional behavior, combined with *facilitating conditions*, determines the actual use of the technology (Figure 4.5). In this study, the UTAUT was used to develop the interview guide for the focus groups and to analyze the focus group transcripts.

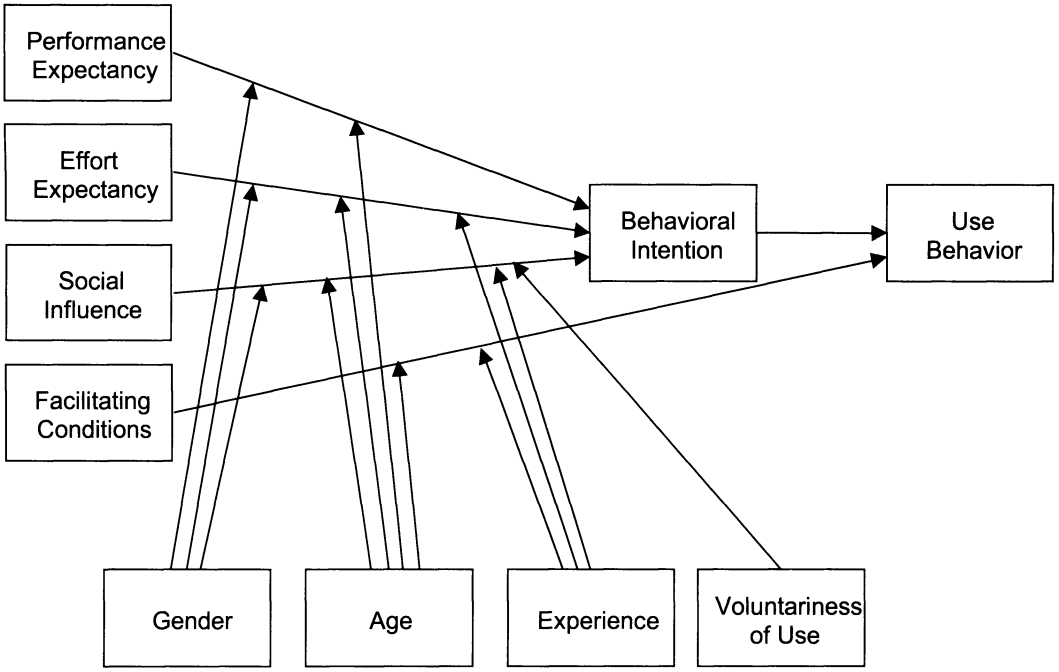

FIGURE 4.5: Unified Theory of Acceptance and Use of Technology (UTAUT) model adopted from (Venkatesh, Morris, Davis, & Davis, 2003). Copyright © 2003, Regents of the University of Minnesota. Used with permission.

4.4.3.2 Data collection and analysis

Sampling strategy Twelve purposefully selected physicians (with specialties in HIV or TB treatment) and all the eleven nurses at the HIV outpatient clinic were invited to participate in the formative evaluation study. The venue for the physician focus group was a lunch session on a weekday when the physicians had regularly scheduled consultation meetings. Despite the researchers' effort in finding a suitable time and place for the meeting, only four of twelve physicians attended. The nurses were invited to participate in a separate session. Their focus group was held at one of their education meetings where ten of the eleven nurses attended.

Data collection An interview guide was developed that covered the following themes: content and functionality, usability (perceived usefulness and perceived ease of use), influence on work practices, and acceptance (Appendix Study IV). The themes and questions were based on the UTAUT model and the findings from Study I. A functional version of the eviTMA prototype proposed in Study III was developed using Justinmind Prototyper Pro software (version 5.6.0, Justinmind, San Francisco, USA).

The author gave a brief presentation to the focus groups in which the background and purpose of the project were explained. This presentation was followed by a demonstration of the CDS prototype. Two facilitators (not research team members) conducted the

focus group discussions. They were familiar with the project and had participated in developing the interview guide. The primary facilitator led the discussion and determined that all topics were covered. The assistant facilitator helped maintain the focus on the topics and tracked the time. Screenprints of the CDS prototype were available in printed form to support the discussion. The author, who participated in both focus groups as an observer, was available to answer questions about the functionality of the prototype. The focus groups lasted for approximately 1 hour and were audio recorded.

Data analysis As in Study I, thematic analysis was used for the qualitative data analysis (Braun & Clarke, 2006). The author transcribed (in Swedish) the focus group discussions verbatim. Three researchers were actively involved in the data analysis. The researchers read the transcripts several times to immerse themselves in the material. Unlike the analysis in Study I, both deductive and inductive approaches were used to abstract and categorize the data.

In the deductive phase, a coding scheme was defined for the four UTAUT constructs, which are defined below (Venkatesh et al., 2003, p. 447ff):

- *Performance expectancy* is defined as "the degree to which an individual believes that using the system will help him or her to attain gains in job performance".
- *Effort expectancy* is defined as "the degree of ease associated with the use of the system".
- *Social influence* is defined as "the degree to which an individual perceives that important others believe he or she should use the new system".
- *Facilitating conditions* are defined as "the degree to which an individual believes that an organizational and technical infrastructure exists to support use of the system".

Two researchers, working independently, coded the transcripts. An inter-rater reliability comparison was made to evaluate the coding consistency, which was substantial (Cohen's kappa coefficient, 0.68). Disagreements were resolved in discussions with the third researcher before proceeding with the inductive analysis.

In the inductive phase, the author recoded the transcripts using open coding. The purpose was to identify potential benefits and concerns. Within each UTAUT construct, meaning units were identified and labeled with a descriptive code. The codes were grouped in categories. The three researchers discussed and developed themes and sub-themes.

4.5 ETHICAL CONSIDERATIONS

Ethical approval for the four studies was obtained from the Research Ethics Committee at Karolinska Institutet: Studies I, III, IV (case number 2010/238–31/4); Study II (case numbers 2006/1445–31/2 and amendment 2012/155–32). The participants in Studies I, III, and IV gave their written consent to participate in the research project. They were informed verbally and in writing about the purpose of the research and how the data would be analyzed and reported. The interviews and focus groups were audio recorded. Audio files were stored safely at multiple locations. During transcription, the names of the interviewees as well as names of others mentioned in the interviews were replaced with unique codes to ensure confidentiality during analysis. The identity of the participants was not revealed in the presentation of the findings. The data collected and analyzed in Study II was stored in a database management system. Personal identifiers (names or personal identification numbers) of patients were stored separately in a remote location. All analyses were conducted and reported on a group level. Consent was not required of the patients in the study.

5 FINDINGS

This chapter is structured as follows: section 5.1 describes the identified challenges from the contextual analysis (Studies I and II); section 5.2 describes the design and formative evaluation of a CDS prototype for drug therapy guidelines for HIV-related TB treatment (Studies III and IV).

5.1 CONTEXTUAL ANALYSIS

5.1.1 Study I

HIV and tuberculosis coinfection: A qualitative study of treatment challenges faced by care providers.

The aim of this study was to understand challenges faced by nurses ($n = 7$) and physicians ($n = 6$) in the treatment of patients with HIV-related and TB disease.
The researchers identified the following five challenges based on analysis of the interviews:

1. *Complexity inherent to HIV/TB co-treatment.* The care providers reported that the concomitant treatment of HIV/TB coinfection is complex. Their main difficulties occur in diagnosing TB and in choosing a treatment strategy. The choice of treatment strategy depends on the patient's condition and drug regimen. It is essential to avoid drug-drug interactions between antiretroviral drugs and anti-TB drugs. Adverse drug reactions, which are common, often require treatment modifications.

2. *Clinical knowledge and task standardization.* The care providers lacked confidence in their clinical knowledge and experience with HIV-related TB treatment. They thought the clinical practice guidelines provided only limited support. They were also concerned about the lack of task standardization. The care providers said they wanted computer-based guideline support although some of them were concerned about the potential risks of such support.

3. *Care coordination and collaboration.* The uncertainty about the division of responsibilities created problems with care coordination and collaboration. Because of the occasional unavailability of staff, it was sometimes difficult to have access to expertise. The care providers also said the communication and collaboration among care team members and between the HIV and TB clinics should be improved.

4. *Information management.* The information systems did not provide optimal information management. Insufficient structure, overview, and information access in the EHR can create a high cognitive workload and can mean additional time and effort are required. The care providers thought these problems could be alleviated by the use of automatic reminders.

5. *Engaging patients in their treatment.* Because the complex treatment is arduous for patients, it was difficult for the care providers to engage patients (using motivating discussions) in their prescribed treatment. Language and cultural barriers contributed to this difficulty. The care providers wanted improved routines for discussing treatments with patients.

The following comment points to the importance of continuous assessment and re-evaluation of treatment decisions and plans:

> … Because it is somewhat disturbing if you have your treatment plan and then suddenly 'Well, no, now this doesn't apply anymore. Now there is a liver side effect. Then we have to start over from the beginning.' So that is also part of the whole process when some patients don't follow this train that just rolls on; it is also a part of the treatment that we have these problem situations that sometimes require quite a bit of thinking. (Physician)

In my opinion, the 'train that just rolls on' is a mechanical and inflexible metaphor for patient treatment. It captures the rigidity of care protocols formulated only as a set of discrete treatment options. In reality, complex patient treatment is sometimes unpredictable – treatment does not always follow a permanent track. In the research reported on in this thesis, I often reflected on this railway metaphor. Even when treatment guidelines seem inflexible, care providers should have space to use their judgment in real world settings. The issue is whether it is possible to design a CDS system that recommends specific workflow routines and yet still allows for flexibility in their adoption.

5.1.2 Study II

Tuberculosis among HIV-infected patients in Stockholm, Sweden, 1987–2010: treatment outcomes and adverse reactions.

The aim of this study was to describe HIV-related TB treatment in the studied context by taking a quantitative perspective on a population of patients diagnosed with and treated for HIV-related TB disease in the Stockholm County Council from 1987 to 2010.

5.1.2.1 The study population

The number of patients in the study population was $N = 127$: 26 patients were in the early cohort and 101 patients were in the late cohort. Twenty-nine countries were represented by the patient group. The majority of the patients were born outside Sweden, mainly in Sub-Saharan African countries (85% in the early cohort and 88% in the late cohort). The percentage of female patients was 23% ($n = 6$) in the early cohort and 49% ($n = 49$) in the late cohort ($p = 0.02$). Figure 5.1 is a bar chart, split by geographic origin, of the annual

number of cases during the study's timeframe. The patients' median age was similar in the cohorts: 35 years (IQR 30–40) in the early cohort and 36 years (IQR 32–43) in the late cohort.

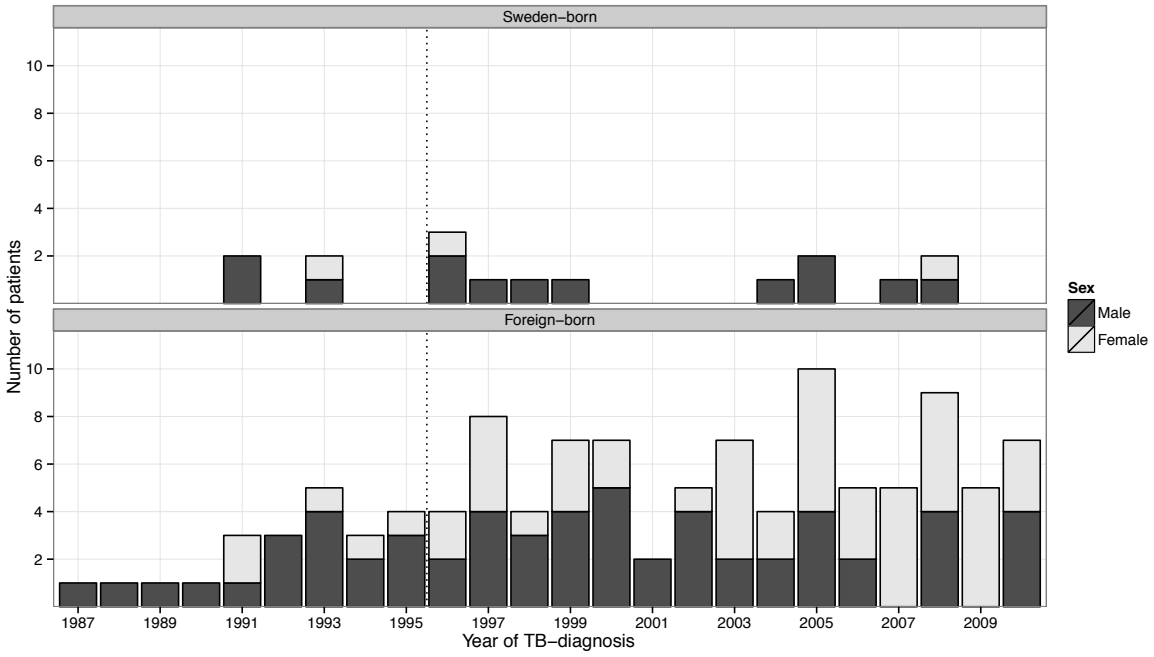

FIGURE 5.1: Bar chart of HIV/TB coinfection cases 1987–2010 ($N = 127$), split by geographic origin. The dotted vertical line represents the stratification of the study population into two cohorts, the *early cohort* (1987–1995, $n = 26$) and the *late cohort* (1996–2010, $n = 101$). Figure used with permission from the publisher (Study II).

5.1.2.2 Anti-TB treatment outcomes

The successful anti-TB treatment outcomes for patients increased from 65% ($n = 17$) in the early cohort to 91% ($n = 92$) in the late cohort ($p = 0.002$). This change is evidence of the improved treatment in the late cohort when cART was available. In the late cohort of patients, 31% ($n = 31$) were on cART at the time of the TB diagnosis, 45% ($n = 45$) initiated cART at a median of 1.9 months (IQR 0.9–3.9) after TB diagnosis, and 25% ($n = 25$) had no concomitant cART. Adverse reactions leading to treatment modifications occurred in 23% ($n = 23$) of patients in the late cohort; of these patients, 96% ($n = 22$) were on concomitant cART. Liver side effects ($n = 8$) were the most frequent manifestation of adverse reactions. The median duration of successful anti-TB treatment, excluding patients with TB in the central nervous system, was 8 months in the early cohort and in the late cohort.

5.1.2.3 Predictors of anti-TB treatment success and adverse reactions

The influence of cART in anti-TB treatment, including the occurrence of adverse reactions, was analyzed in 99 of the 101 patients in the late cohort (two patients whose treatment outcomes could not be evaluated were excluded). The results of the multivariable logistic regression analyses are presented in Table 5.1. Treatment success was associated with cART and a CD4 cell count >200 cells/μL. The initiation of cART after the TB diagnosis was positively associated with adverse reactions.

TABLE 5.1: Results of the logistic regression analyses in Study II: factors related to treatment success and adverse reactions to anti–TB treatment for patients with HIV-related TB, diagnosed 1996 or later (N=99). Table used with permission from the publisher (Study II).

	Successful treatment outcomes ($N = 99$)			
Variables	Yes ($n = 92$) n (%)	No ($n = 7$) n (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
cART				
Yes	72 (78)	3 (43)	4.8 (1.0–23.2)	13.3 (1.5–114.8)[a]
No	20 (22)	4 (57)	Reference	
Sex				
Female	47 (51)	1 (14)	6.3 (0.7–54.1)	5.9 (0.5–71.1)
Male	45 (49)	6 (86)	Reference	
Age, y				
≤ 37	57 (62)	1 (14)	9.8 (1.1–84.6)[a]	9.8 (0.9–105.0)
> 37	35 (38)	6 (86)	Reference	
CD4 count, cells/μL				
≤ 200	51 (55)	6 (86)	Reference	
> 200	41 (45)	1 (14)	4.8 (0.6–41.7)	17.2 (1.2–236.6)[a]
	Adverse reactions to anti–TB treatment ($N = 99$)			
Variables	Yes ($n = 23$) n (%)	No ($n = 76$) n (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
cART				
Before TB diagnosis	3 (13)	27 (36)	2.6 (0.2–26.3)	2.8 (0.3–29.3)
After TB diagnosis	19 (83)	26 (34)	16.8 (2.1–135.6)[b]	13.3 (1.6–112.4)[a]
No cART	1 (4)	23 (30)	Reference	
Sex				
Female	13 (57)	35 (46)	1.5 (0.6–3.9)	1.0 (0.3–3.0)
Male	10 (44)	41 (54)	Reference	
Age, y				
≤ 37	18 (78)	40 (53)	3.2 (1.1–9.6)[a]	2.7 (0.8–9.0)
> 37	5 (22)	36 (47)	Reference	
CD4 count, cells/μL				
≤ 200	18 (78)	39 (51)	3.4 (1.2–10.1)[a]	1.8 (0.5–6.2)
> 200	5 (22)	37 (47)	Reference	

[a] $p < 0.05$. [b] $p < 0.01$. Abbreviations: cART, combined antiretroviral therapy. OR, odds ratio.

5.2 DESIGN AND FORMATIVE EVALUATION OF A CDS PROTOTYPE

5.2.1 Study III

Modeling evidence-based drug therapies: the eviTMA clinical decision support framework applied to HIV/TB care.

The aim of this study was to design a CDS prototype to support care providers in the adoption of guidelines for HIV-related TB treatment.

5.2.1.1 Knowledge base model

The knowledge base model described below is a structural representation of drug therapy guidelines for the treatment of HIV-related TB that is based on the eviTMA framework. The model is represented as a UML class diagram (Figure 5.2).

The class diagram is organized into three packages: `TMA_Recommendations`, `Drugs`, `Tests`. The `TMA_Recommendations` package contains the concepts and relationships to represent drug therapy guidelines. The `Drugs` package represents a drug repository. Individual drugs are described with their intended and unintended effects, as well as interactions with other drugs. The `Tests` package represents a test repository with defined order sets.

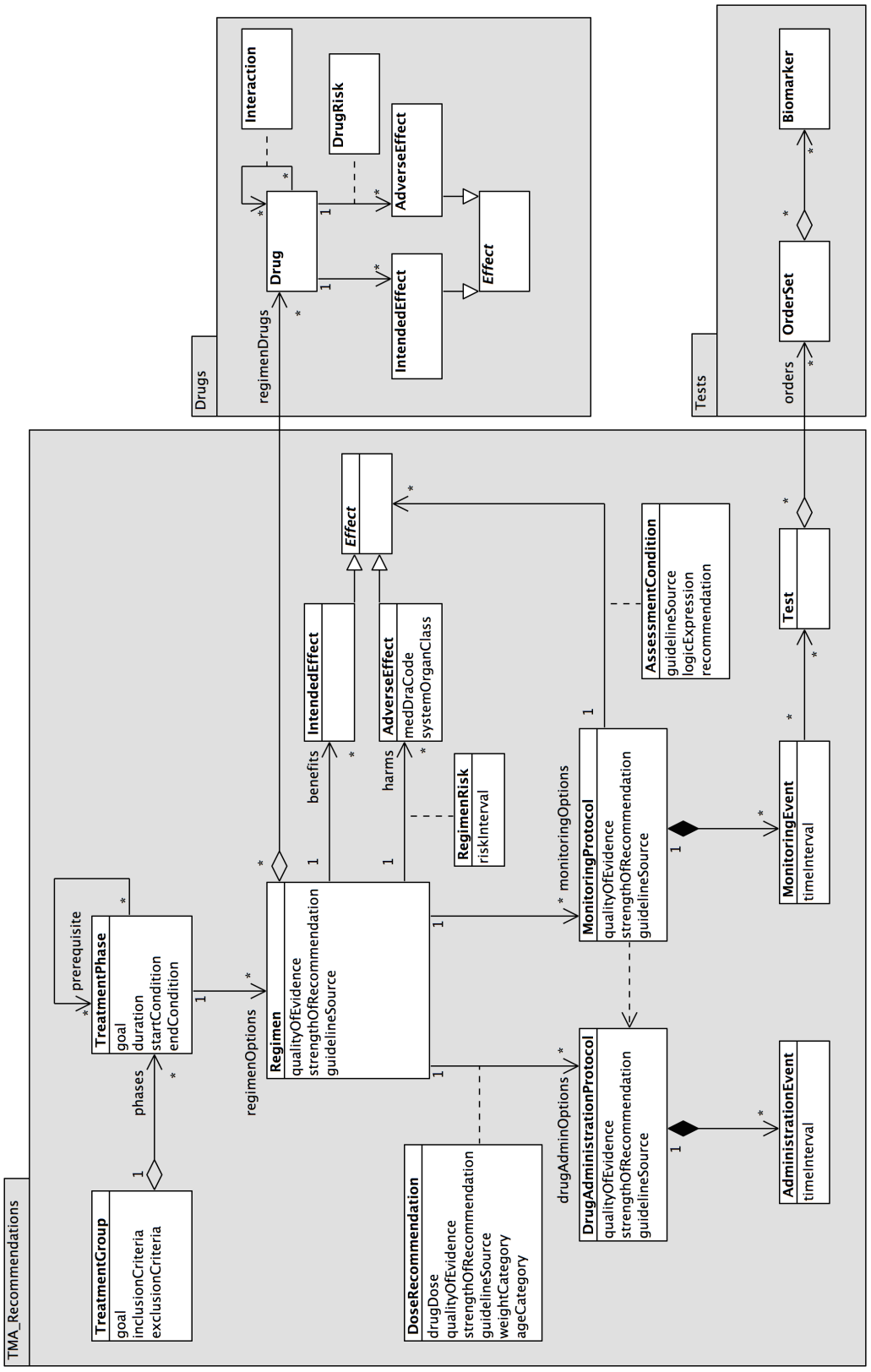

FIGURE 5.2: UML class diagram of the eviTMA knowledge base model of drug therapy guidelines for HIV-related TB treatment. The model is organized into three packages: `TMA_Recommendations`, `Drugs`, `Tests`. The classes represent guideline concepts and medical domain knowledge.

The concepts of the eviTMA model are described below:

`TreatmentGroup` Specifies the eligibility criteria for a subset of drug therapy recommendations. An example of a `TreatmentGroup` would be *Extrapulmonary TB with involvement of the central nervous system.* The drug therapy recommendations that belong to this `TreatmentGroup` apply to patients who meet the eligibility criteria.

`TreatmentPhase` Specifies a distinct treatment phase. Anti-TB treatment starts with an *intensive phase* of two months. If the treatment goal of this phase is achieved, the *continuation phase* can be initiated. Hence, the intensive phase is a prerequisite for the continuation phase.

`Regimen` Specifies a recommended drug regimen and its evidence rating — for example, *Rifampin-based anti-TB therapy combined with an efavirenz-based antiretroviral therapy (Evidence rating AII).* The `Regimen` is composed of `Drugs`, which are retrieved from the `Drug` repository. Intended and adverse effects of the `Regimen` are represented by the associated classes `IntendedEffect` and `AdverseEffect`. Recommended protocols for drug administration and monitoring are represented by the associated classes `DrugAdministrationProtocol` and `MonitoringProtocol`.

`DrugAdministrationProtocol` Specifies a drug administration and dosage schedule for a `Regimen`. For example, during the intensive phase daily therapy is recommended. The protocol consists of `AdministrationEvents` that specify the administration time intervals.

`MonitoringProtocol` Specifies a monitoring schedule for a `Regimen`. It consists of `MonitoringEvents`.

`MonitoringEvent` Specifies the time interval for a monitoring event. Further, the `MonitoringEvent` is associated with the class `Test`.

`Test` Specifies a test that should be performed at a `MonitoringEvent`. A test can be a procedure (e.g., *vision control*). It can also be a blood test (e.g., a *liver function test*). The latter is composed of `OrderSets` (e.g. *liver transaminases*).

`OrderSet` Specifies the `Biomarkers` that should be tested. For example, a *liver transaminases* `OrderSet` is composed of the liver enzymes aminotransferase (AST) and alanine aminotransferase (ALT).

`AssessmentCondition` This is an association class between the classes `MonitoringProtocol` and `Effect`. Its purpose is to define conditions for assessing monitoring results. It specifies a logic expression and recommends an action if the expression evaluates as `true`. For example, an AST test result >5 times the upper limit

of normal may indicate a drug-induced liver injury (Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents, 2013). Hence, an alert should be issued to notify care providers that an adverse drug reaction is suspected.

`DrugRisk` This is an association class between the classes `Drug` and `AdverseEffect`. It specifies the estimated risk interval of an adverse effect. For example, *hepatobiliary disorders* are common (>1% and <10%) for the anti-TB drug isoniazid (FASS, 2002), but uncommon (>0.1% and < 1%) for the anti-TB drug rifabutin (FASS, 2008).

`RegimenRisk` Like `DrugRisk`, but the association is between the classes `Regimen` and `AdverseEffect`.

5.2.1.2 GUI prototype

A screenprint of the GUI prototype is presented in Figure 5.3.

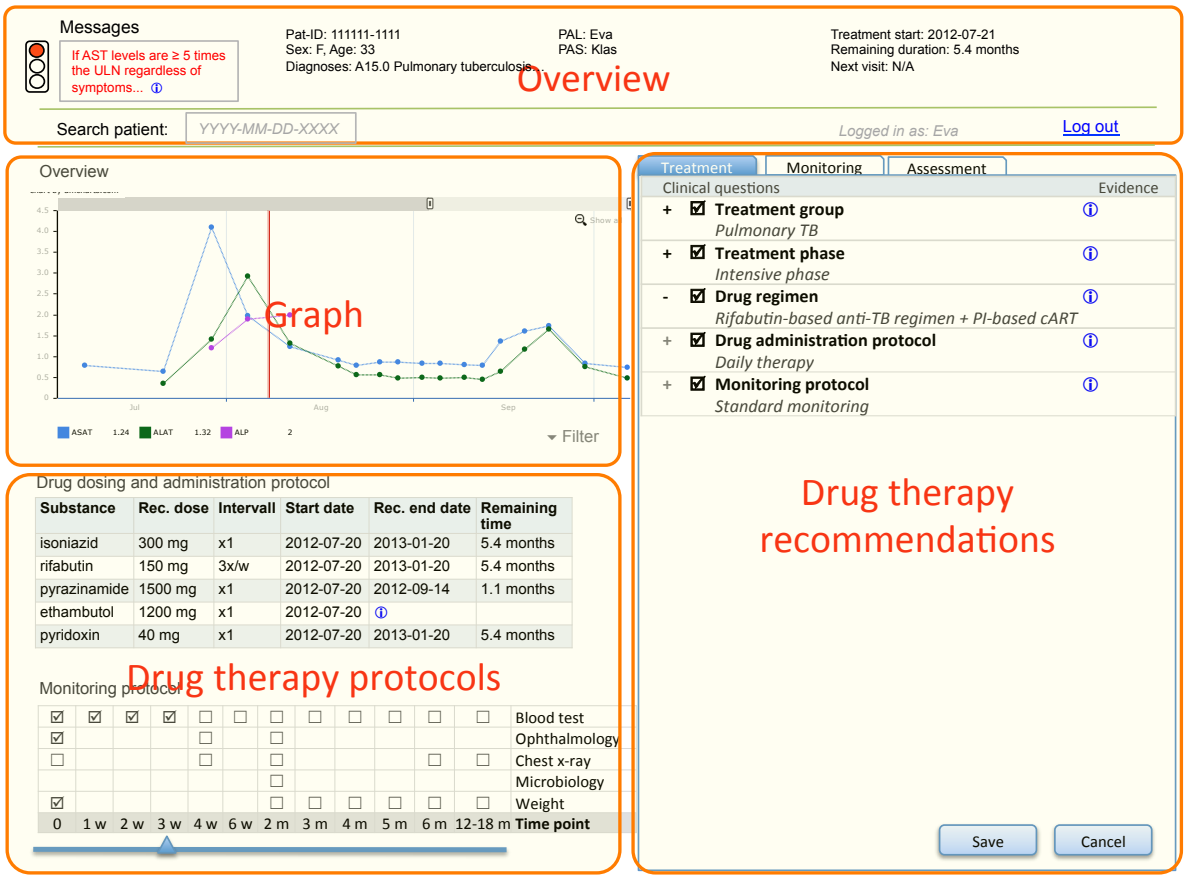

FIGURE 5.3: Graphic user interface (GUI) mockup of the eviTMA CDS prototype for HIV-related TB. The GUI consists of four main components: overview, graph, drug therapy recommendations, drug therapy protocols.

The GUI prototype has four components:

1. The *overview* component contains a summary of patient characteristics and information about the treatment. A message field lists all issued alerts and reminders (e.g., lab results that should be examined).
2. The *graph* component depicts a graphic treatment overview. Laboratory parameters, drug therapy, and event markers for qualitative examinations and results are graphed on a timeline.
3. The *drug therapy recommendations* component is the core CDS component. Drug therapy recommendations are presented in a panel with three tabs (treatment, monitoring, assessment).
4. The *drug therapy protocols* component depicts the recommended drug administration and monitoring protocols. These are only shown if a drug therapy has been chosen for the patient.

The drug therapy recommendations component is the only interactive part of the CDS prototype. The following sections describe its sub-components: treatment, monitoring, and assessment.

Treatment The *Treatment* sub-component is intended mainly for physicians (Figure 5.4). The physician follows a five-step process when deciding on a treatment strategy (1. selection of treatment group, 2. selection of treatment phase, 3. choice of drug regimen, 4. choice of drug administration protocol, and 5. choice of monitoring protocol). In each step, the physician is presented with all potentially applicable options that are contained in the guideline model. A static recommendation layer presents guideline content, independent of patient characteristics. Alternative treatment options are presented in a tree-view structure, ordered by quality of evidence and strength of recommendations. The tree-view allows the user to browse guideline content. The dynamic recommendation layer provides patient-specific recommendations by annotating non-supported treatment options with a warning symbol.

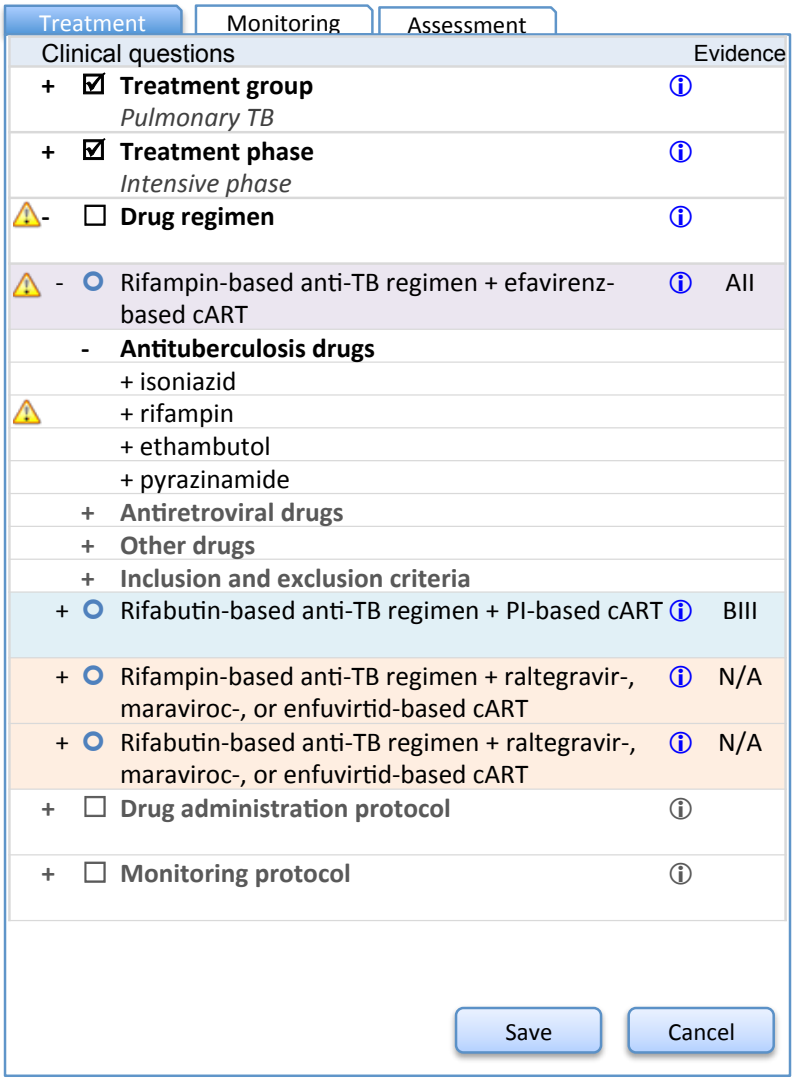

FIGURE 5.4: Graphic user interface mockup of treatment recommendations, which is intended mainly for physicians. The drug therapy options, ordered by quality of evidence and strength of recommendations, represent the guideline content independent of patient characteristics (i.e., static recommendation layer). The warning icons illustrate patient-specific recommendations (i.e., the dynamic recommendation layer).

Monitoring The *Monitoring* sub-component is intended mainly for nurses (Figure 5.5). Drug administration and monitoring protocols become available after the physician has saved a drug therapy choice to file. In the Monitoring component, detailed monitoring checklists can be accessed for each recommended monitoring event.

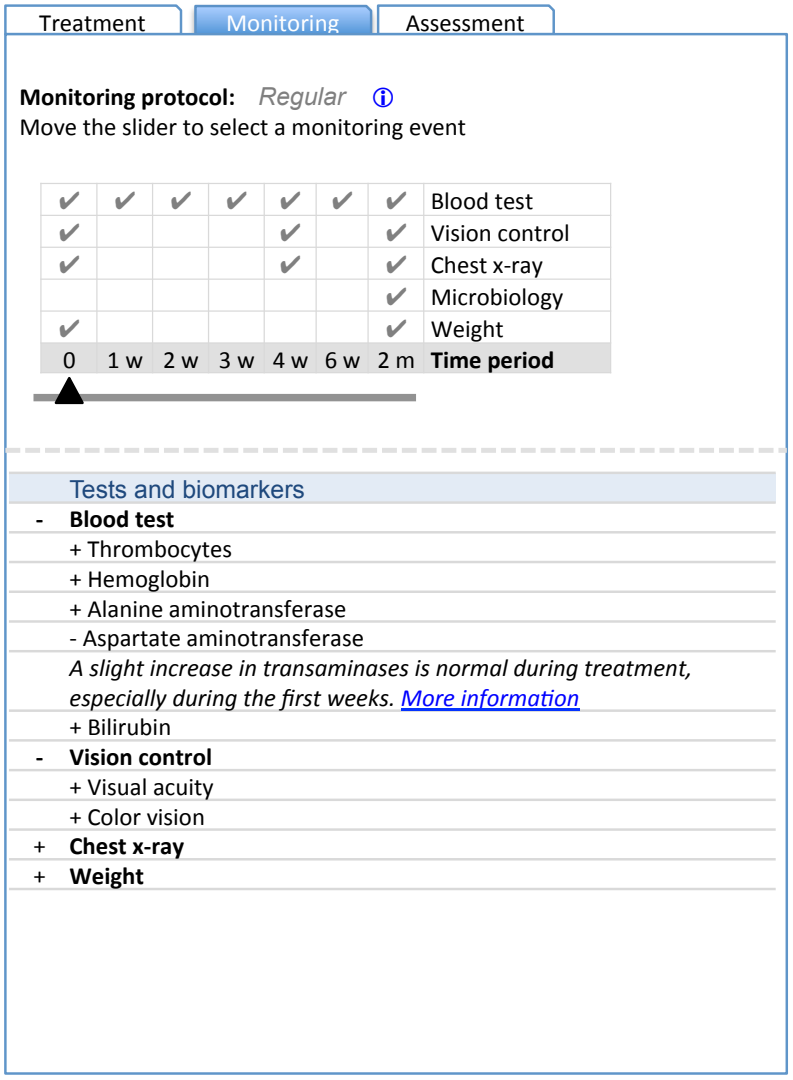

FIGURE 5.5: Graphic user interface mockup of monitoring recommendations, which is intended mainly for nurses. A monitoring protocol with recommended monitoring events for the duration of the drug regimen is presented. The user selects a monitoring event in the protocol by moving the horizontal slider. A list of recommended monitoring tests is presented in a tree-view. The user can browse information related to the individual tests and biomarkers.

Assessment The *Assessment* sub-component is intended for both nurses and physicians (Figure 5.6). It provides support for adverse drug reactions (ADRs). An *ADR-browser* lets the user explore relationships between drugs and ADRs. Furthermore, alerts are shown if an ADR is suspected based on monitoring results.

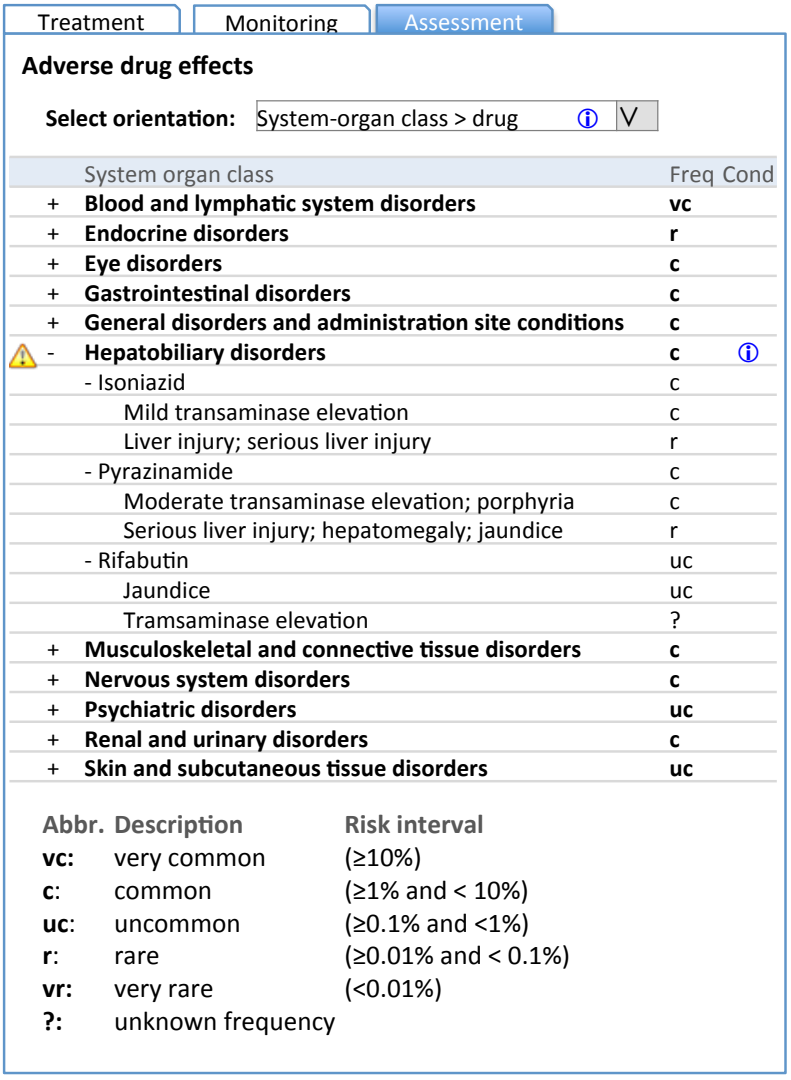

FIGURE 5.6: Graphic user interface mockup of assessment recommendations, which is intended for nurses and physicians. The user can explore relationships between drugs and adverse drug reactions (ADRs) that could potentially occur, based on available pharmacovigilance data. The warning icons represent alerts, which appear if an ADR is suspected based on monitoring results.

5.2.2 Study IV

Qualitative evaluation of the eviTMA clinical decision support model applied to HIV/TB care.

The aim of this study was to evaluate the conceptual design of the CDS prototype that resulted from Study III with physicians ($n = 4$) and nurses ($n = 10$) at the HIV outpatient clinic.

Based on the demonstration, all care providers said they intended to use the CDS prototype. In the following sections, the principal benefits and concerns identified in the

analysis are presented for the four UTAUT constructs of *performance expectancy*, *effort expectancy*, *social influence*, and *facilitating conditions*. Each construct is introduced with a representative comment from the focus groups.

5.2.2.1 Performance expectancy

> Off hand, I would say that I would get a better feeling of what I do- and an overview of the patients, especially when we take over each other's patients. (Physician)

The study participants identified several potential benefits of the eviTMA CDS prototype that could lead to improvements in job performance. Generally, they thought that the prototype contributed to a better overview of their patients' treatments. They also thought this would improve control of treatments. The following specific uses were identified: support in patient involvement and education, educational support for care providers, collaboration support, and support for quality improvement work.

The care providers perceived that visualization of treatment progress, as well as protocols and checklists, were CDS features that could improve their performance. Treatment recommendations and alerts, as well as the adverse drug reaction feature, produced mixed opinions. Mainly, the care providers were concerned about possible overdependence on the CDS system (i.e., the concern that the users of the prospective CDS system would not think independently). They emphasized that the recommendations should not be too rigid or too steering. On the other hand, they viewed alerts (e.g., in the case of inappropriate medication) as a potential benefit. The only feature not considered beneficial was the opportunity to read and write user comments in the CDS (e.g., to comment about a treatment decision or an alert)[1]. One reason was that this functionality would conflict with the use and purpose of the EHR system.

5.2.2.2 Effort expectancy

> Nurse: The advantage is if you are new at a workplace, it is very simple to just click on this.
>
> Facilitator: Tell us more.
>
> Nurse: If I were completely new and I didn't know so much about TB treatment, like – what should be done now? It is so simple – now I can see which tests I should perform, which drugs the patients should receive. It is simple to just step in.

[1]The commenting functionality was not in CDS mockups that resulted from Study III. It was added as an additional feature in the functional prototype in Study IV

Because the care providers did not have the opportunity to test the prototype in a hands-on situation, they were not able to express any strong opinions about its ease of use. However, based on what they had seen, they thought it appeared easy to use.

They thought that the visualization of treatment progress contributed to a better overview, which could reduce the time needed for information searches. They appreciated having all the information they needed in one place. On the other hand, they emphasized that too much functionality or information in the system might create cluttering (e.g., the commenting functionality). The care providers also noted that their active use of the CDS system would increase their workload, due to the additional data entry required.

5.2.2.3 Social influence

> [...] the key is to convince the physicians. (Nurse)

Social influence is defined as "the degree to which an individual perceives that important others believe he or she should use the new system" (Venkatesh et al., 2003). The researchers did not identify this type of social influence in their analysis. However, they did identify a type of professional dependency. Nurses were concerned that the success of the system depended on the attitudes and behavior of the physicians.

5.2.2.4 Facilitating conditions

> It takes quite a long time for experts to agree on this document [clinical practice guideline] that should be written in present time – there is a constant reevaluation of what is optimal. (Physician)

As the above comment illustrates, the issue of knowledge management and maintenance was discussed. The care providers revealed concerns about this issue. Different providers and organizations may have different routines and opinions about best practice recommendations. Furthermore, such recommendations may change rapidly. Someone must update the system, which takes time and requires financial resources.

A main concern of the care providers was the integration of the CDS system with the EHR system. If not well integrated, the addition of a new system could also contribute to substantial increase in administrative workload and potential inconsistencies between systems. Another concern related to the legal requirements of the documentation and the use of data.

6 DISCUSSION

This thesis proposed eviTMA as a CDS framework for modeling treatment, monitoring, and assessment recommendations for evidence-based drug therapies in HIV-related TB care. The framework supports adherence to recommended workflow routines while still allowing for flexibility in their adoption. A user-centered approach was used to examine the challenges that care providers face in treating HIV-related TB (Studies I and II), to design a CDS prototype that addresses these challenges (Study III), and to formatively evaluate the CDS prototype (Study IV). The four studies were conducted at the HIV outpatient clinic at the Karolinska University Hospital, Huddinge, in Stockholm. In Studies I, III, and IV, physicians and nurses at the hospital informed and formatively evaluated design sketches and the CDS prototype.

6.1 CHALLENGES AND NEEDS IN HIV/TB CARE

6.1.1 HIV-related TB in the study setting

This thesis showed that TB among HIV-infected individuals in Stockholm County Council is strongly linked to migration from highly endemic countries (Study II), which is generally the case in northwestern EU countries (Pimpin et al., 2011). A previous study has shown that the majority of AIDS cases in Sweden are 'late testers' (i.e., the time interval between the HIV and AIDS diagnosis is ≤3 months). Immigrants represent the largest, increasing proportion of these patients (Brännström, Akerlund, Arneborn, Blaxhult, & Giesecke, 2005). The group of late testers poses medical challenges because immunosuppression is associated with higher mortality (Palella et al., 2003).

In the study setting (the late cohort, years 1996 to 2010), the majority of patients were immunosuppressed (CD4 cell count <200 cells/μL) and not on antiretroviral therapy when diagnosed with TB (Study II). The initiation of a combined cART and anti-TB treatment was associated with successful treatment outcomes, which was defined as a successfully completed treatment without any registered TB recurrence within at least one year's follow-up. However, adverse reactions to anti-TB treatment (including IRIS) were common, especially among those who initiated cART following their TB diagnosis, which is consistent with previous research (Blanc et al., 2011). In the current Swedish national guidelines for HIV treatment, PI-based cART is a recommended first-line alternative after the NNRTI efavirenz, in combination with anti-TB treatment (Referensgruppen för antiviral terapi, 2014). The most common cART in the study setting was PI-based, which has been associated with a higher risk of adverse reactions than efavirenz-based cART (Dos Santos et al., 2013).

The above findings indicate that HIV-related TB care in the study setting is complex, and patients are at high risk of developing adverse drug reactions, that require careful monitoring.

6.1.2 Clinical practice guidelines (awareness and adherence)

The care providers in this thesis faced challenges that arose because of gaps in clinical knowledge, guidelines with limited usefulness, and a lack of task standardization (Study I). The low number of yearly reported cases of HIV-related TB in the study setting (on average fewer than 10 cases annually) (Study II), made it particularly challenging for care providers to follow guidelines and recommended routines by memory. These findings, which are consistent with the gaps in TB expertise reported by Moro et al. (2005) in Italy (also a low-incidence setting), indicate the need for better guideline-based support.

The challenges related to insufficient knowledge about guidelines are not unique to low-incidence settings. Two recent review studies have reported on this lack of awareness of anti-TB treatment guidelines (van der Werf et al., 2012) and the poor guideline adherence (Langendam, van der Werf, Huitric, & Manissero, 2012). Almost all continents were represented in these studies although the first study included no European countries. van der Werf et al. (2012) found that incomplete knowledge of anti-TB treatment regimens and anti-TB treatment duration was common. In the study setting of this thesis, variation in the duration of anti-TB treatment was generally longer than the guidelines recommended (Study II). This issue was not examined in the research for this thesis. However, the care providers said they needed support with treatment initiation and with monitoring routines (Study I). Langendam et al. (2012) found that because inappropriate drug prescriptions in anti-TB treatment are common, there is a risk of resistance to drug therapy. The authors of the study emphasize the need to improve the implementation of treatment guidelines.

6.1.3 Information management

The National Academy of Engineering (US) and Institute of Medicine (US) Committee on Engineering and the Health Care System (2005) emphasize the critical role of information and communication technology (ICT) in improving the quality of patient care. In Sweden, ICT is well integrated in the organizational development of healthcare (Ministry of Health and Social Affairs, 2011). In particular, Sweden is a leading country in the development and use of quality registries (Sousa, Bazeley, Johansson, & Wijk, 2006). The InfCare HIV quality registry, which is one of the most highly developed registries in Sweden, aims to provide decision support by visualizing clinical data related to antiretroviral therapy (Rosén, 2010). At the time of this research, there was no support for HIV-related TB treatment or guidelines that the care providers wanted (Studies I and IV). The care providers said that the EHR system did not provide support sufficient to efficiently follow up anti-TB treatment (Study I). This lack of support resulted in time-consuming searches for information and a high cognitive workload for care providers.

6.1.4 Collaboration and communication

In the studied setting, physicians and nurses collaborated in care teams, which is a recommended practice in chronic care management (Wagner, 2000). Multi-professional care teams are associated with improved quality of HIV care although they are also associated with a decrease in physician continuity (Rodriguez, Marsden, Landon, Wilson, & Cleary, 2008). Therefore, Rodriguez et al. (2008) emphasize the need to facilitate coordination within care teams. Collaboration challenges were identified both within care teams and between the HIV and TB clinics (Study I).

The care providers also experienced communication challenges with patients that mostly were the result of cultural and language barriers. This problem was further complicated by some foreign patients' distrust of interpreters. Kulane, Ahlberg, and Berggren (2010) relate immigrants' fear of interpreters in the studied medical setting and their reluctance to share information with care providers to immigration policies. Strategies are needed to address barriers related to cultural/social stigmas, fear of sharing information, and fear of using interpreters.

Tools to educate and engage patients in their medical treatment have been successfully implemented in other areas of chronic care (Hvitfeldt et al., 2009). A graphic visualization of a patient's treatment-related data, as well as recommended treatment protocols, may facilitate communication, although such methods do not solve problems related to immigration policies.

6.2 DESIGN OF THE EVITMA FRAMEWORK

CDS systems for drug prescriptions usually address treatment initiation or monitoring (Pearson et al., 2009). Such systems rarely address the entire treatment process. The eviTMA framework covers the entire treatment process, from treatment initiation to completion. The high-level representation of drug therapy guidelines consists of three linked components: treatment, monitoring, and assessment. This structure is intended to reflect generic drug therapy concepts that support the activities of collaborating care teams.

Trustworthy guidelines should "provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations" (Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, 2011, p. 26). For each recommendation, a clear description of potential benefits and harms should be provided. The eviTMA framework explicitly models the logical relationships between drug regimens and adverse effects. The care provider can thereby receive notification when an adverse effect has occurred including information on the drugs that may have been the cause.

6.2.1 Support for workflow, admitting flexibility

A guiding principle in the design of the eviTMA framework was to support adherence to guideline recommendations while still allowing for flexibility in their adoption. Different approaches have been proposed that would permit more flexible use of guidelines when integrated in CDS systems.

Intention-based guideline formalisms (e.g., ASBRU and GASTON/GASTINE) are approaches intended to achieve flexibility in computer-based guideline representations (Miksch, Shahar, & Johnson, 1997; de Clercq, Blom, Hasman, & Korsten, 2000; Latoszek-Berendsen, de Clercq, van den Herik, & Hasman, 2009). These formalisms are based on the task network model (TNM), which means they represent guidelines as structured task sequences. However, different pathways to a goal are supported by specifying the intentions of guideline recommendations. These are examples of active systems with a critiquing communication style (see section 1.5). Critiquing support is provided through interpreting the intention of the physician's actions and comparing that with the intention of the recommended care plan in the computer-interpretable guideline (CIG) model, based on patient-specific characteristics (Latoszek-Berendsen et al., 2009; Miksch et al., 1997).

Critiquing systems have more often been associated with success than consulting systems (Sintchenko et al., 2007). However, Bouaud et al. (2006) suggest that for complex care, such as chronic disease management, on-demand consulting systems that allow for flexibility are more appropriate. Séroussi, Bouaud, and Antoine (2001) propose a rigid representation of guidelines as decision trees, which is a representation used in the OncoDoc guiding system for breast cancer treatment. Séroussi et al. (2001) stress the physician's autonomy in controlling the medical decision process. Each node in the decision tree represents a decision parameter; the tree leaves represent treatment plans. Flexibility during guideline execution is achieved by allowing the user to navigate through the decision parameters, step by step. No automated advice is provided. Hence, this is a passive system with a consulting communication style (see section 1.5)

The eviTMA CDS prototype combines the benefits of these guideline formalisms in order to provide both passive and active support in a consulting communication style (Studies III and IV). The user initiates the CDS functionality when drug therapy guidance is needed. While the eviTMA CDS prototype uses a consulting style, the user is not guided through the decision-making process step by step, which may be a hindrance to care providers (Patkar & Fox, 2008). Rather, a combination of static and dynamic recommendations is used to give the user access to all drug therapy options augmented with patient-specific recommendations (see Figure 5.4). The static recommendations present all the treatment options that are contained in the guideline, ordered by evidence rating (i.e., a rigid guideline representation). The dynamic recommendations provide patient-specific warnings for non-recommended options. Once a drug regimen has been selected for the patient, the CDS system can provide active support for the assessment of

monitoring results. The rules that trigger alerts are specific to the chosen drug regimen and to the monitoring protocol. This procedure may reduce the risk of alert fatigue.

6.3 FORMATIVE EVALUATION OF THE EVITMA CDS PROTOTYPE

The care providers found the eviTMA concept intuitive because the treatment, monitoring, and assessment activities are representative of their clinical work (Study IV). All care providers indicated their intention to use the eviTMA CDS prototype, which was demonstrated as a potential extension or add-on to the existing InfCare HIV quality registry.

6.3.1 Benefits of a holistic overview

Sittig et al. (2008) state that one of the greatest CDS challenges is to generate summaries of patient data that allow care providers to make a quick and adequate evaluation of the patient's condition. One of the main identified benefits with the eviTMA CDS prototype was the overview provided by the graphic visualization of both patient data and drug therapy recommendations. Forsman, Anani, Eghdam, Falkenhav, and Koch (2013) show how the integration of information from different sources into a holistic overview can support antibiotics decision-making in the intensive care unit. The findings in this thesis indicate that this type of holistic overview is also desirable in an ambulatory setting for the treatment of complex patient conditions. In such conditions, care providers must keep track of many parameters. The additional guideline-based support for treatment selection and monitoring provided in the eviTMA CDS prototype may be particularly useful for long-term planned care. The monitoring protocol, for example, provides an overview of the treatment process and supports care planning and coordination. Martínez-García, Moreno-Conde, Jódar-Sánchez, Leal, and Parra (2013) demonstrate how the addition of a social network component may further support care provider collaboration and shared decision-making in the care of patients with multiple comorbidities.

6.3.2 A support for patient engagement

Varonen, Kortteisto, Kaila, and EBMeDS Study Group (2008) identified potential facilitators and barriers to the implementation of CDS systems among physicians in Finland. They found that these physicians were worried that CDS systems may have negative effects on the physician–patient relationship. The care providers described in this thesis thought that the eviTMA CDS prototype could enhance the relationships between care providers and patients, especially if there were language barriers. This opinion is likely related to their current use of the InfCare HIV quality registry in patient discussions.

Ovretveit et al. (2013) describe how the continuous development of the Swedish quality registry for arthritis has resulted in multiple uses of the quality registry and has also enabled greater patient involvement in shared decision-making. Because of the integrated

guideline support in the eviTMA CDS prototype, the care providers also discussed the potential for generating drug administration and monitoring reminders for patients. Studies indicate a generally positive attitude among patients to text message reminders for HIV or TB treatment in both high- and low-income settings (Person, Blain, Jiang, Rasmussen, & Stout, 2011; Albino et al., 2014). A future development with patient reminders may be a viable strategy for enhancing patients' adherence to HIV-related TB treatment recommendations.

6.3.3 Concerns related to workload, autonomy, and CDS integration

Two possible implementation barriers to CDS systems are the extra workloads caused by CDS systems and the threat to physicians' autonomy; CDS systems should be flexible and reliable (Varonen et al., 2008). These concerns also appeared in the evaluation of the eviTMA CDS prototype.

The care providers were concerned about the extra workload caused by the eviTMA CDS prototype. While the holistic overview of the prototype could increase productivity, the interaction with the CDS prototype would require additional data entry, especially by physicians. Therefore, the nurses were concerned that the success of a future CDS system depended on its acceptance and use by the physicians. Kilsdonk et al. (2011) report that physicians are more willing to use a CDS system if they think the effort to use it is worthwhile and if they feel in control of it. On the other hand, insufficient integration of guideline-based CDS systems with clinical workflow is a major obstacle to their use (Maviglia et al., 2003).

The combination of static and dynamic drug therapy recommendations in the eviTMA CDS prototype aims to respect care providers' autonomy and to avoid errors. While the care providers thought that these recommendations could have educational value, they were apprehensive that their clinical judgment would be subordinated to the recommendations. This situation could lead to overdependence on CDS. Because the CDS prototype was limited to evidence-based treatment regimens, the physicians said that complex cases may not be supported. Therefore, if the CDS prototype does not fully account for the complexity of the patient's condition, it may not always provide proper guidance. Awareness of such risks is vital in order to prepare for and deal with the potential unintended consequences of CDS (E. M. Campbell, Sittig, Guappone, Dykstra, & Ash, 2007).

The care providers emphasized that CDS systems must be reliable and stable. Wright and Sittig (2008) describe different architectures for integrating CDS systems with clinical information systems. Standalone systems, which require double registration of clinical data, can cause increased workloads and data inconsistencies between systems. Both results may jeopardize patient safety. Double registration is a current problem with Swedish quality registries (Rosén, 2010). Furthermore, there are legal constraints on the use of quality registry data for CDS. These are important problems that require solutions prior to CDS system implementation in clinical practice.

6.3.4 Knowledge management requirements

The care providers pointed to the length of time it takes experts to agree on and develop new guidelines. They wondered who would take responsibility for updating and maintaining a future CDS system based on the eviTMA framework. Kim, Makhene, Sizemore, and Hafner (2012) emphasize that clinical development and research should be conducted in parallel so as to reduce delays in implementation. These concerns are especially important in healthcare where medical treatments develop rapidly, as is the case in HIV-related TB treatment. As of 2010, more than twenty antiretroviral agents had been licensed (Palmisano & Vella, 2011). Additional drugs have become available since then (Arribas & Eron, 2013). The European Medicines Agency recently approved bedaquiline as a new anti-TB drug (European Medicines Agency, 2014). Bedaquiline was the first new anti-TB drug to be approved in 40 years. Today there are several drugs in late phases of clinical development (World Health Organization, 2013a).

Ash et al. (2012) emphasize that before the implementation of CDS systems in an organization, a knowledge management program should be established for their local adaptation, implementation, and maintenance. Ideally, clinical knowledge management is best conducted in multi-professional teams that use web-based tools and repositories for collaborative knowledge development and maintenance (Sittig et al., 2010).

Patel, Allen, Arocha, and Shortliffe (1998) have shown that collaboration between clinical experts and computer scientists results in more consistent representations of computer-interpretable guidelines than either professional group could achieve independently. Rather than translating narrative guidelines into computer-interpretable representations, Goud, Hasman, Strijbis, and Peek (2009) propose a process of parallel guideline development and formalization in which knowledgeable experts and appropriate tools are involved early on. Access to domain knowledge and formal verification are also central requirements of the process. The Observational Health Data Sciences and Informatics (OHDSI) collaborative recently established a workgroup for the development of a standardized drug safety knowledge base that models and maintains the effects of medical products (Boyce et al., 2014). An integration of such a knowledge base in the eviTMA framework could support guideline developers as well as care providers by ensuring that the most recent knowledge about the potential harmful effects of individual drugs are always available.

6.3.5 Potential uses of eviTMA

Ash et al. (2010) state that developers of CDS systems may have a different understanding of such systems than care providers. Therefore, these authors recommend defining CDS systems more broadly to reflect the perceptions of their users. The care providers in this thesis envisioned a multi-functional CDS system: a decision support tool; an educational support tool (for them and the patients); a collaborative tool for care providers;

a communication tool (e.g., for patient discussions and consultation meetings); and a quality improvement tool. Furthermore, the care providers wanted support based on the eviTMA framework for other patient conditions, for example, for TB mono-infection. In short, these various uses of the eviTMA CDS prototype that the care providers describe reflect their complex need for support tools.

6.4 METHODOLOGICAL CONSIDERATIONS

Qualitative and quantitative methods were used in combination in this thesis to gain a deeper understanding of the studied phenomena. A purposeful sampling strategy was used in Studies I, III, and IV of this thesis in order to involve care providers with varying expertise and experience with HIV or TB treatment. This strategy was selected to capture multiple views from the care providers. Neither the number of participants nor their roles in the various research phases were specified prior to the research; thus, the design can be said to be emergent. In the following sections, issues related to the trustworthiness of the research and limitations of the individual studies are discussed.

6.4.1 Trustworthiness

This section discusses the trustworthiness of the research by addressing issues related to the truth value, consistency, applicability, and neutrality of the findings (Dahlgren, Emmelin, Winkvist, & Lindhgren, 2007). The following sub-sections address these criteria, with references to both the quantitative and the qualitative research paradigms. Each of these issues is introduced with a question, adapted from (Dahlgren et al., 2007, Table 1, p. 45).

6.4.1.1 Have we really measured what we set out to measure? – the truth value issue

The aim was to identify various challenges and opportunities related to HIV-related TB treatment (Studies I and II), and to design and formatively evaluate a CDS prototype (Studies III and IV). Triangulation of methods was used to explore these challenges and opportunities from different perspectives. For example, both qualitative (Study I) and quantitative (Study II) methods were used to explore and describe challenges in the study setting. The findings from Study II corroborated the challenges identified in Study I. The findings from Study IV further emphasized the need to address these challenges.

Prolonged engagement, negative case analysis, and member checking are also important for establishing truth value in qualitative research (Lincoln & Guba, 1985). These research methods are inherent in a user-centered design approach. In this thesis, the author's engagement with the research setting lasted throughout the four studies. In becoming acquainted with the setting and its culture, the author could guard against preconceived assumptions. Rapport and trust were established with the care providers,

some of whom were actively involved in the thesis project on several data collection occasions. The design of the CDS prototype was refined iteratively as new knowledge was acquired. This design process also enabled member checking as some of the participants were involved in several phases of the design.

6.4.1.2 Would the findings be repeated if the research were replicated in the same context with the same subjects? – the consistency issue

Because the researcher is the data collection instrument in qualitative research, Dahlgren et al. (2007, p. 50) claim that the likelihood of producing the same results in repeated data collections (i.e., reliability) is "absurd". Knowledge is constructed in the interaction between the researcher and the participant (Kvale & Brinkmann, 2009, p. 2). Nevertheless, certain research measures may support the consistency of findings. For example, in this research, the use of interview guides ensured all topics of interest were covered and leading questions in interviews and focus groups were avoided. Moreover, an external researcher was involved to discuss the analysis in Study I, and three researchers were involved in the analysis in Study IV. Triangulation of methods, which was applied to the overall thesis design, also contributes to consistency (Patton, 2002).

6.4.1.3 How applicable are our results to other subjects and other contexts? – the applicability issue

Qualitative research aims for generalization of research findings based on a "reasoned judgment" about the applicability of these findings in other settings (Kvale & Brinkmann, 2009, p. 262). The reader may make this type of generalization when the findings are derived from a thick description of the original research (Lincoln & Guba, 1985). In this research, the applicability of the findings was strengthened through a clear description of the study sample and contextual factors of the setting. Some identified challenges are strongly and specifically linked to this research setting (e.g., collaboration patterns). However, different identified challenges may be found in other (although similar) settings.

The applicability of the eviTMA framework to clinical guidelines for chronic conditions other than HIV-related TB disease can be assumed based on the three generic activities of treatment, monitoring, and assessment that the framework builds on. However, further investigation is required to test this assumption. Similarly, the applicability of the GUI prototype to other settings requires testing and evaluation.

In Study II, the limited size of the study population, the diversity of the patient group, and the long period of study are the principal factors that challenge the generalizability of the findings. Due to the limited population of HIV/TB coinfected patients in the research setting, random sampling was not feasible (or needed). Patients were selected based on inclusion criteria, which can be compared to criterion sampling in qualitative research

(Patton, 2002, p. 238). The primary purpose of the study was not to generalize but rather to describe the patient population in the research setting and to identify opportunities for CDS.

6.4.1.4 To what extent are the findings affected by personal interests and biases? - the neutrality issue

Preconceived ideas are biased only if the researcher fails to reveal them (Malterud, 2001). Clearly, one of the author's preconceived ideas in this research was that CDS could address the challenges in HIV-related TB treatment. This assumption also affected the type of challenges in focus, namely those that refer to information processing that ICT can support. In particular, the focus was on tasks that are cognitively challenging. However, neutrality was achieved and maintained via the discussions and analyses by the multiprofessional research team.

6.4.2 Limitations of the four studies

6.4.2.1 Study I

Interviews were selected as the best available instruments for understanding how care providers think and for identifying the challenges they face. The critical decision method was selected because it aims to identify the cognitive elements in decision making (Crandall et al., 2006). The author's assumption was that the identification of cognitive elements important in care providers' decision-making would be useful in specifying the design requirements of a CDS prototype. The interview technique relies on the identification of critical incidents, which are characterized by a sequence of events and by critical decisions that have occurred during a limited period of time (Crandall et al., 2006). Time pressure usually plays an important role in these incidents – hence, the term *critical*.

In the conduct of the interviews, two problems were encountered: 1) Most care providers had limited experience with HIV-related TB treatment; and 2) Critical incidents as described above were not easily identified. Nevertheless, the resulting CDM-inspired interviews provided insights into the challenges care providers face in the treatment of HIV-related TB beyond decision-making.

6.4.2.2 Study II

In epidemiological studies, there is a risk of both *random errors* and *systematic errors* (Rothman, 2002). These possible errors are of relevance in the retrospective design in Study II, which aimed at identifying factors associated with success in anti-TB treatment and with adverse reactions to anti-TB treatment. Due to the limited size of the study population, random differences between individual cases may wrongly have strengthened

or weakened explored associations. It is also possible that existing associations between variables could not be detected due to lack of statistical power. Possible *systematic errors* of concern in this study were *information bias* and *confounding* (Rothman, 2002).

Information bias A first step in the analysis was to classify patients into different groups based on the data collected. For example, patients were classified in a group *with adverse reactions* or in a group *without adverse reactions*. The occurrence of adverse reactions was determined on the basis of physicians' clinical documentation in medical records. Because the physicians may have evaluated and documented these reactions differently, it is possible some patients may have been misclassified.

Measurement instruments and techniques are likely to have improved during the years of the study (from 1987 to 2010). Hence, variations in measurement accuracy may also have resulted in patient misclassifications. This concern is of particular relevance for the classification of immunosuppression (based on CD4 cell counts), which was used as a predictor variable in the multivariate logistic regression analyses.

Confounding The two potential confounders we identified as most important – age and gender – were controlled by multivariable analysis. Owing to the limited size of the study population, it was not feasible to include more control variables in the analysis. For example, the potential confounder of ethnicity was not controlled although the study population was a multi-ethnic group.

Hence, while the explanatory power of Study II may be weak, several of the study's results confirm the existence of the challenges described by the care providers: the variation in socio-demographic background of patients, the variations in treatment duration, and the observed frequency of adverse reactions.

6.4.2.3 Study III

A user-centered approach may involve users at the evaluation stage only or, as co-designers, also in the design stage (Preece, Rogers, & Sharp, 2002). In this thesis, the users were not co-designers although they provided feedback on the research team's design proposals. While a more participatory approach may be desirable, it also requires a good deal of time by participants. Such time commitments may be limited in health care settings (see (Frykholm, Lantz, Groth, & Walldius, 2010; Lyng & Pedersen, 2011)).

Design sketches and class diagrams were modeled and discussed by the research team. One-to-one discussion meetings between the author and the study participants elicited user requirements and discussions of the desired functionalities. Involving care providers in this way can help overcome usability concerns (Kilsdonk et al., 2013). The purpose of the iterative design and evaluation cycles was to detect problems and to refine the design based on the acquisition of new knowledge.

6.4.2.4 Study IV

Some researchers have pointed to the risk of publication bias with CDS system evaluations. In two review studies, CDS system success was related to the system under evaluation by its developers (Garg et al., 2005; Roshanov et al., 2013). This risk may be applicable in Study IV. However, as Study IV was a formative evaluation, its purpose was not to draw conclusions about the predicted success of the system but rather to improve its design.

The focus group is a useful research method for the evaluation of group members' intentions related to the use of a system based on low-fidelity prototypes (van Velsen et al., 2008). The presentation of an interactive prototype allowed the researchers in this study to discuss its predicted usefulness and issues related to its ease of use. The application of the UTAUT as an analytical framework enabled the researchers to explore known determinants of behavioral intention as well as the use of technology. According to the UTAUT, gender, age, experience, and voluntariness of use are moderating factors that can strengthen or weaken the influence of these determinants (Venkatesh et al., 2003). However, moderating factors were not controlled for in the focus group evaluation; only one participant was male, none had any experience with the system, and voluntariness of use was not discussed. These factors were not addressed because the study was not intended to analyze associations. The focus was on identifying the potential benefits and concerns with the demonstrated CDS prototype.

7 CONCLUSIONS

This thesis concludes that strategic measures are needed that address some of the challenges care providers face in the treatment of HIV-related TB. The eviTMA framework proposed in this thesis may be a viable approach for modeling evidence-based drug therapy guidelines that can be integrated with the clinical workflow of care teams. The eviTMA CDS prototype provides a holistic overview of alternative drug therapy options, their potential benefits and adverse effects, and recommended monitoring routines. The prototype supports adherence to recommended routines and yet still allows for flexibility in their adoption. The integration of the eviTMA CDS, with its graphic visualization of patient data in a CDS prototype, led the care providers to list multiple uses of the prototype: as a decision support and educational support tool (for care providers and patients), as well as a tool for communication, collaboration, and quality improvement.

Several technical, organizational, and legal issues require consideration when CDS systems are implemented and used. It is also necessary to deal with the risk of overdependence on CDS and with the care providers' concerns about increased workloads. Moreover, a knowledge management group that includes both clinical and technical experts should be established when a CDS system is adopted. Such a group can maintain and update the system's knowledge base with medical domain knowledge and evidence-based guidelines.

7.1 IMPLICATIONS FOR PRACTICE

The conceptual design of the eviTMA framework was evaluated in a CDS prototype for HIV-related TB treatment. It is recommended that healthcare organizations planning to adopt the eviTMA framework in CDS systems for modeling evidence-based guidelines for other chronic conditions consider the following:

- The eviTMA framework is intended for integration with an electronic health record (EHR) system or other clinical information system that can provide access to patient data.[1]
- A guideline modeling expertise group should be established for CDS content development and maintenance. The guideline modeling process includes the following main steps: 1) selection of guidelines, 2) identification of treatment, monitoring, and assessment recommendations in the guidelines, 3) translation of guideline recommendations to a computable format, which requires resolving any ambiguities and vagueness in the narrative guidelines, 4) validation and verification of the resulting guideline model, 5) implementation, maintenance, and versioning of guideline content. The modeling process can be facilitated by linking to existing knowledge repositories, such as drug repositories, adverse drug reaction repositories, and order set repositories.

[1] Legal constraints for providing patient-specific decision support require consideration.

- The design and development of a CDS system requires the involvement of representative users at all stages. Their needs inform the system design and establish the criteria for its evaluation. This involvement of users may lead to early detection of usability problems and possible unintended consequences. CDS content and functionality require proper integration in the technical, organizational, and clinical contexts.

7.2 FUTURE RESEARCH

Future research may evaluate the usability of the eviTMA framework in a clinical setting. In this effort, researchers may investigate the development of tools and strategies that support the development, maintenance, and sharing of guideline content, as well as the implementation and transferability of guideline-based CDS systems. As the design of CDS systems is informed by users' needs, implementation in different contexts may require adaptation. Finally, the effects on practitioner performance, as well as patient outcomes, call for additional evaluations aimed at continuous improvement.

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APPENDIX STUDY I

TASK DIAGRAM INTERVIEW GUIDE (SWEDISH)

Bakgrund

- Hur lång erfarenhet har du inom hiv/tb-vården?
- Hur uppskattar du din erfarenhet av att behandla patienter med dubbelinfektion (hiv och tb)?
- Ungefär hur många patienter med dubbelinfektion behandlar du per år?

Patientbesök

- Behandlingsstart
    1. Tänk på vad du gör när du gör en behandlingsplan. Kan du beskriva vilka steg eller deluppgifter som ingår? Det borde helst vara mindre än 6, men mer än 3 uppgifter.

- Återbesök
    1. Vilka är de övergripande målen med uppföljningsbesöken?
    2. Hur uppnås dessa mål?
    3. När och hur gör man ändringar i behandlingsplanen?

- Av de steg/deluppgifter du precis har identifierat, vilka uppgifter ställer störst krav på kognitiva färdigheter? Med det menar jag bedömning, värdering, problemlösning, beslutsfattande.

Avslutning

- Har du något mer du vill tillägga?

CDM INTERVIEW GUIDE (SWEDISH)

Intro

Hur lång erfarenhet har du inom hiv/tb vården?

1 - Fall identifiering

OBS! Berättelse om vad som *hände* och *gjordes*, inte förklaringar om vad och hur man *bör* göra.

Kan du berätta om en utmanande situation du har upplevt?

Har det hänt att du har missat/glömt något?

Har det hänt att du har fattat ett felaktigt beslut?

2 – Tidslinje

Har jag förstått det här rätt?

Var på tidslinjen ska jag sätta detta?

Beslutspunkter, ändringar i förståelse, probing-punkter, gap i historien, glapp i tidslinjen, konceptuella språng, anomalier/överraskningar, fel, flertydiga ledtrådar

3 - Fördjupning

Mål och prioriteringar	*Vad hade du för specifika mål vid det här tillfället?* *Vad var viktigast att göra vid det här tillfället?* *Vad ville du uppnå?*
Ledtrådar	*Vad lade du märke till?* *Hur visste du att du behövde fatta ett beslut?* *Hur visste du vad du behövde göra?* *Vad hade du för bekymmer?* ***Vad ledde till ditt beslut?***
Standard procedurer	***Är detta ett typiskt fall?*** *Finns det riktlinjer för denna typ av fall?*
Erfarenhet	*Vilken erfarenhet krävdes?*
Konceptuell/ Mental modell	*Tänkte du på möjliga konsekvenser?* ***Vad för mental bild skapade du över situationen?*** ***Hur bedömde du situationen?*** ***Hur skulle du sammanfatta situationen så här långt?***
Informations-tillgång	***Vilken information hade du?*** ***Hur fick du tillgång till informationen?***
Informations-användning	*Vilken information **använde** du?* *Vilken information var viktigast och varför?* *Var det svårt att hantera informationsmängden? Beskriv situationen i detalj.*
Hjälpmedel/ Stöd	***Bad du om någons hjälp eller använde något hjälpmedel?*** *Hur visste du att du kunde lita på det stöd du fick?*

Möjligheter	*Fanns det några alternativ?*
	Varför förkastades dessa alternativ?
Osäkerhet	*Var du osäker över tillförlitligheten eller relevansen av informationen du hade till ditt förfogande?*
	Var du vid något tillfälle osäker över beslutets lämplighet?
Fel	*Försäkrade du dig att ditt beslut var rätt? Hur gjorde du det?*

4 – Spekulationer

Senior-junior skillnader	***Vad för misstag kan man tänka sig att en junior kliniker skulle ha gjort i en sådan situation och varför?***
	Skulle en junior kliniker ha lagt märke det som du upptäckte?
	Skulle en junior kliniker ha vetat att X måste göras?
Hypoteser	*Om [key feature] hade varit annorlunda, vad för inflytande skulle det ha haft på ditt beslut/bedömning/handlingar/plan?*
Erfarenhet	*Vilken typ av erfarenhet skulle ha varit en fördel i den här typen av situation?*
Hjälpmedel	*Vilken kunskap, information, eller hjälpmedel/teknik skulle ha hjälpt?*

APPENDIX STUDY III

DISCUSSION GUIDE (SWEDISH)

Funktionalitet

- Användning
    a. Under vilka omständigheter skulle du använda ett sådant system?

- Kärnfunktioner
    a. För vilka ytterligare uppgifter/beslut behövs ett stöd?

- Perifera funktioner
    a. För vilka uppgifter/funktioner behövs inget stöd?

Integration i arbetsflödet

- Tidpunkt för beslutsfattande
    a. När i behandlingsprocessen fattas beslut? Före/efter/under patientmöten?
    b. Hur ofta görs uppdateringar/ändringar?

- Beslutsfattandeprocess
    a. Vem är involverad?
    b. Vilka resurser/hjälpmedel används?
    c. Vem måste känna till beslutet?
    d. Hur kommuniceras beslutet?

- Längd på planeringen
    a. Definieras en start- och sluttid på de planer som görs?
    b. Hur definieras och kommuniceras detta?

Avslutning

- Har du något mer du vill tillägga?

APPENDIX STUDY IV

FOCUS GROUP TOPIC GUIDE (SWEDISH)

INTRODUKTION

- Kort introduktion om bakgrunden till projektet och syftet med fokusgruppen
- Carolina beskriver konceptet bakom beslutsstödet samt demonstrerar dess funktion med ett konstruerat patientfall
- Tomas och Jonas startar fokusgruppsdiskussionen
- Samtliga deltagare presenterar sig med namn, beskriver kort sin arbetssituation samt hur de ser på IT i vården

INNEHÅLL/FUNKTIONALITET

- Vilka är era spontana reaktioner när det gäller **beslutstödet**? Hur/varför?
- Är det lätt eller svår att förstå? Hur/varför?
- Är det något som fattas? Är det något som är onödigt? Hur/varför?

Beslutsstödets uppdelning i behandling, monitorering och tolkning

- Vilka är era spontana reaktioner när det gäller beslutstödets **uppdelning i stöd för behandling, monitorering och tolkning**? Hur/varför?
- Är det lätt eller svår att förstå? Hur/varför?
- Är det något som fattas? Är det något som är onödigt? Hur/varför?

Behandlingsrekommendationer

- Vilka är era spontana reaktioner när det gäller beslutstödets funktion för **rekommendationer**? Hur/varför?
- Är det lätt eller svår att förstå? Hur/varför?
- Är det något som fattas? Är det något som är onödigt? Hur/varför?

Monitoreringsstöd

- Vilka är era spontana reaktioner när det gäller beslutstödets **monitoreringsprotokoll/checklista** gällande uppföljning under behandlingen? Hur/varför?
- Är det lätt eller svårt att förstå? Hur/varför?
- Är det något som fattas? Är det något som är onödigt? Hur/varför?

Tolkningsstöd för biverkningar

- Vilka är era spontana reaktioner när det gäller beslutstödets funktion för **tolkning av biverkningar?** Hur/varför?
- Är det lätt eller svår att förstå? Hur/varför?
- Är det något som fattas? Är det något som är onödigt? Hur/varför?

Varningar och åtgärder

- Vilka är era spontana reaktioner när det gäller beslutstödets **funktion att förmedla varningar och rekommendera åtgärder**? Hur/varför?
- Är det lätt eller svår att förstå? Hur/varför?
- Är det något som fattas? Är det något som är onödigt? Hur/varför?

ANVÄNDBARHET

- Används rätt termer och begrepp? Hur/varför?
- Verkar beslutstödets enkelt att använda? Hur/varför?
- Verkar det finnas tillräckligt många olika sätt att göra det ni vill med beslutstödet för att ni ska kunna anpassa den till just ert sätt att använda det? Hur/varför?

INFLYTANDE PÅ ARBETSRUTINER

- Skulle beslutstödet påverka ert sätt att arbeta, före, under och/eller efter ett patientbesök? Hur/varför?
- Tror ni att beslutstödet skulle användas i samtalet med patienten, som ett slags samtalsstöd? Hur/varför?
- På vilket sätt skulle beslutstödet påverka samarbete och samordning av vård? Hur/varför?
- Hur ofta och i vilka situationer skulle ni använda beslutstödet (enskilt, i vårdteam, i vårdsammansträden)? I vilka inte? Hur/varför?

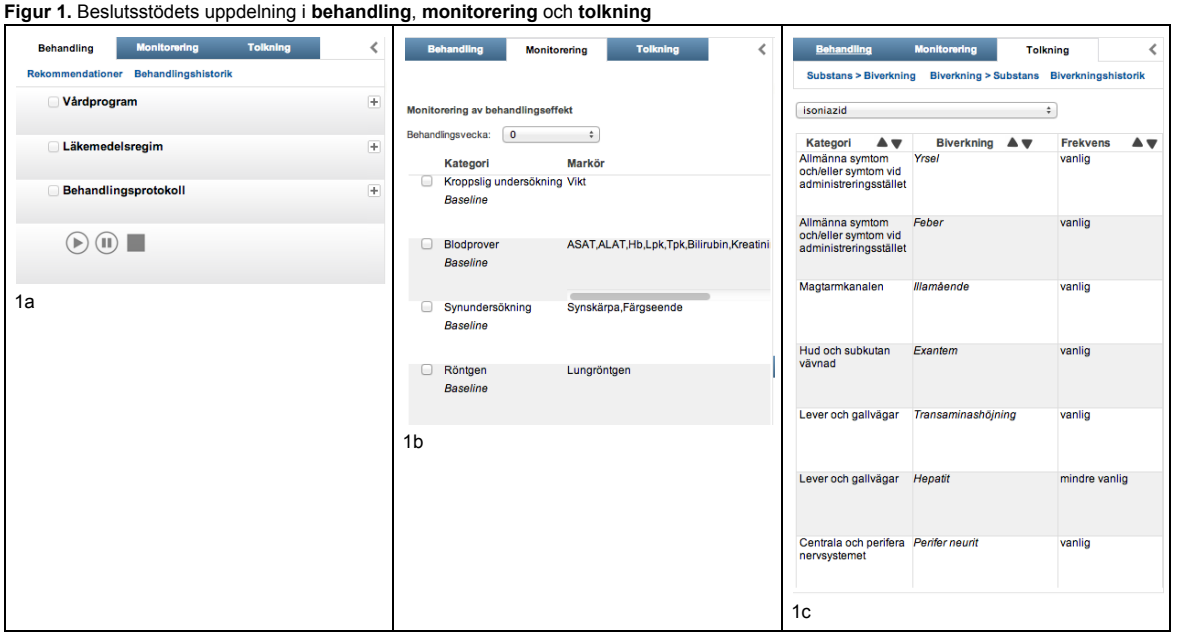
ACCEPTANS

- Vilka nackdelar/fördelar ser ni med att använda använda beslutsstödet?? Hur/varför?
- Vilka hinder kan ni se att det finns för att ni ska använda beslutsstödet? Hur/varför?
- Tror ni att beslutsstödet underlättar tillämpningen av evidensbaserade riktlinjer? Hur/varför?
- Tror ni att beslutsstödet underlättar uppföljningen efter behandlingsstart? Hur/varför?
- Är det en bra idé att använda beslutsstödet för tillämpning av kliniska riktlinjer? Hur/varför?

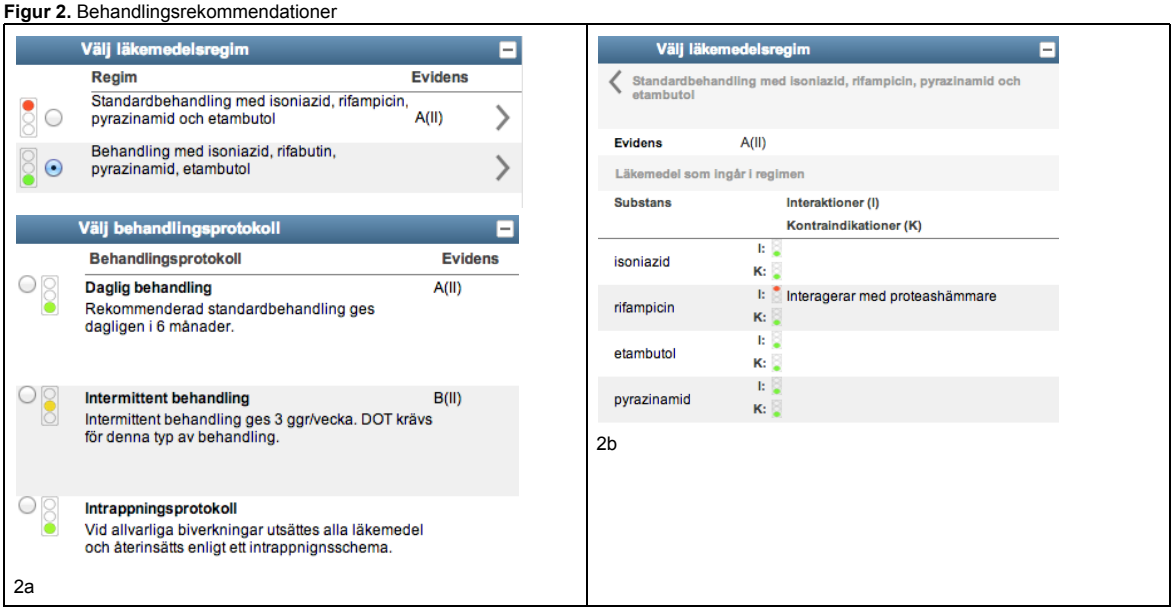
Avslutningsvis, vilka av er skulle idag använda beslutsstödet om det vore tillgängligt? Hur/varför?

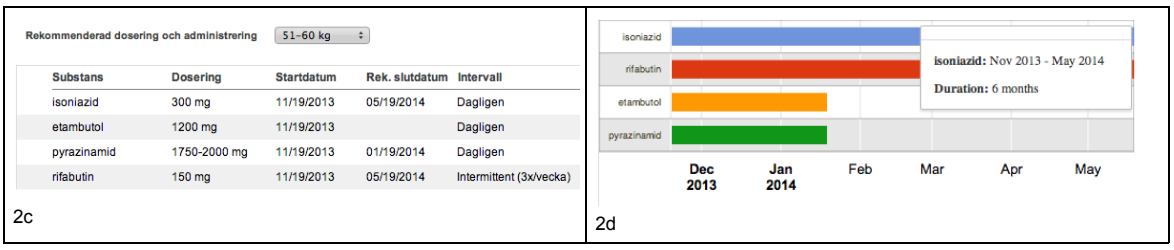
CDS PROTOTYPE SCREEN PRINTS (SWEDISH)

Figur 1. Beslutsstödets uppdelning i **behandling**, **monitorering** och **tolkning**

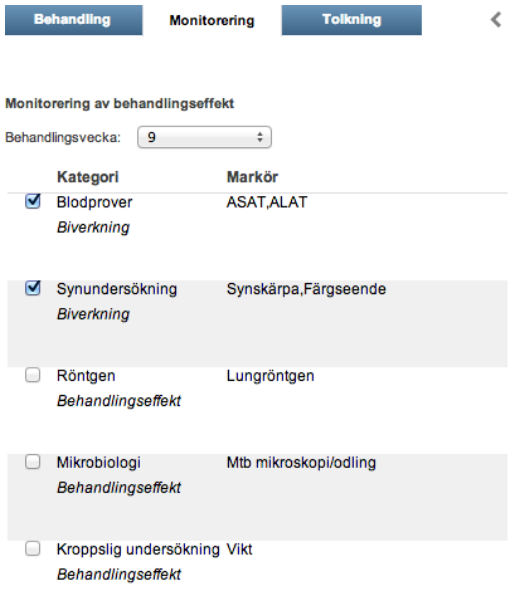


Figur 2. Behandlingsrekommendationer

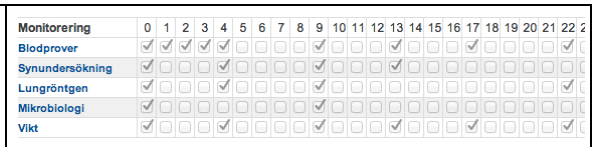




Figur 3. Monitoreringsstöd

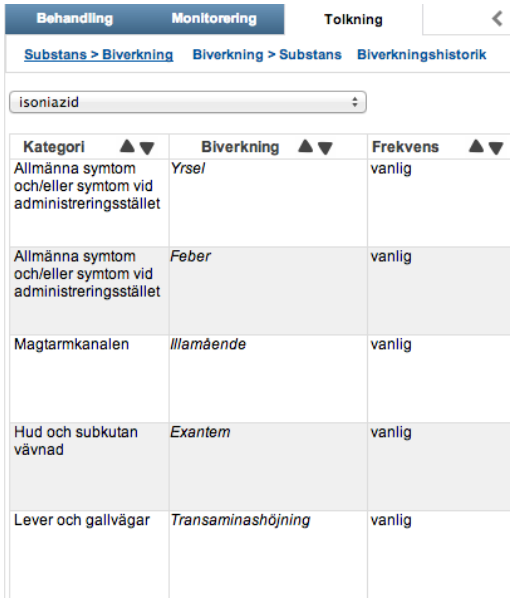


3a

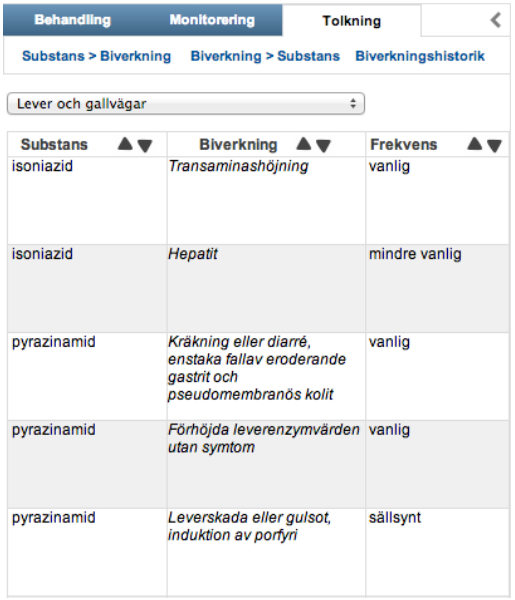


3b

Figur 4. Tolkningsstöd för biverkningar

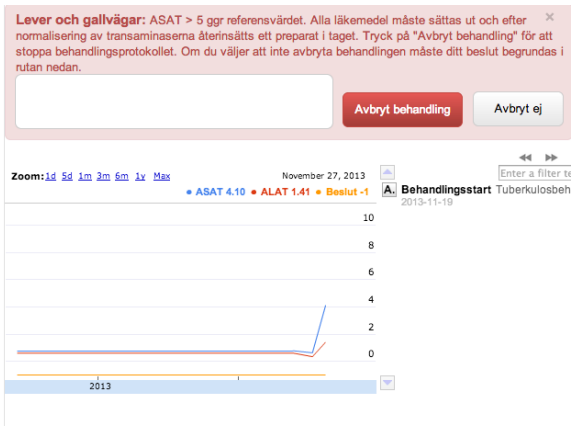


4a



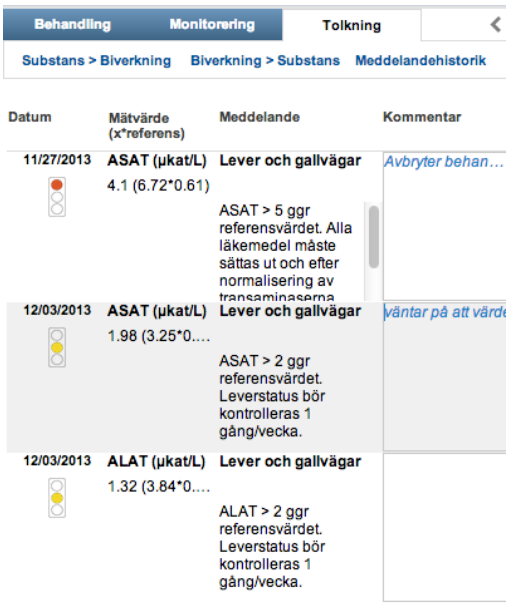
4b

Figur 5. Varningar och åtgärder



5a

5b



5c