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m-Health for antiretroviral treatment support: Evidence from India

Rashmi Josephine Rodrigues

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m-Health for antiretroviral treatment support: Evidence from India

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By

Rashmi Josephine Rodrigues

Principal Supervisor:
Ayesha De Costa
Karolinska Institutet
Department of Public Health Sciences
Division of Global Health

Co-supervisor(s):
Lennart Bogg
Karolinska Institutet
Department of Public Health Sciences
Division of Global Health

Vinod Diwan
Karolinska Institutet
Department of Public Health Sciences
Division of Global Health

Opponent:
Max Petzold
Professor
Gothenburg University, Gothenburg, Sweden
Department of Public Health and Community Medicine
Division of Statistics

Examination Board:
Anna-Karin Hurtig
Professor
Umea University, Umea, Sweden.
Department of Public Health and Clinical Medicine
Division of Global Health

Karin Källander
Associate Professor
Karolinska Institutet, Stockholm, Sweden
Department of Public Health Sciences
Division of Global Health

Nancy Reynolds
Professor
Yale University, USA
Yale School of Nursing
Nothing in life is to be feared, it is to be only understood. Now is the time to understand more, so that we may fear less

- Marie Curie

Dedicated to

my parents, Octavia Menezes and Alban Rodrigues

Their constant support has been an essential driving force in my life!
ABSTRACT

**m-Health for adherence support: Evidence from India**

**Background:** With antiretroviral therapy (ART) HIV infection is now managed like a chronic disease rather than as a fatal disease. Adherence to ART is essential for treatment success. However, the high levels of adherence that are necessary and the multifactorial nature of adherence, make adherence to ART a challenge. The recent years have seen a move towards the development of low cost interventions to support adherence to ART. The ubiquity of mobile phones and the low cost of mobile communication provide an opportunity to support patient adherence with mobile phone based reminders.

**Aim:** To test an mHealth intervention to improve adherence to antiretroviral therapy in HIV patients in South India. Perceptions regarding the intervention and costs of the intervention from the perspective of the national program were studied.

**Methods:** HIV patients in South India receiving the routine standard of antiretroviral treatment and care received adherence reminders on their mobile phones. The reminder comprised of (i) an automated interactive voice response (IVR) call in the local language and (ii) a neutral picture short messaging service (SMS), each received once a week. The intervention was first tested in a cohort with 150 patients already on antiretroviral treatment (Study I). The participants were followed up for one year. All participants received the intervention for first six months along with standard care. For the next six months they received standard of care alone. Adherence was measured periodically using the pill count at follow-ups. A cut off of ≥95% was used to define optimal adherence. A complete case analysis, best and worst case scenario approach were used to assess change in adherence over time. The intervention was subsequently tested in 631 ART naïve patients in a parallel design, randomized trial against standard care over 2 years (Study II). Participants were followed up for a period of two years or till treatment failure (primary end point). Treatment failure was defined as a viral load of >400copies of virus/mm³ of plasma on two occasions at least one month apart. Further, sixteen participants from the RCT participated in a qualitative study that assessed perceptions regarding the intervention with in-depth interviews (Study III). Costs of the intervention and its components were studied with a micro-costing approach (Study IV).

**Results:** Complete case analysis in revealed that the proportion of participants with optimal adherence increased from 85% to 91% in the cohort during the intervention period, the effect persisted for six months after the intervention was discontinued (p=0.016). In the RCT, there was no statistically significant difference in the time to viral failure between the two groups (HR: 0.96; CI 0.64-1.43). There was also no significant difference in the proportions of participants’ adherent to ART between the two groups (IRR: 1.24; CI 0.94-1.63). Participants’ expressed mixed opinions regarding the usefulness of the mHealth intervention in the RCT. IVR calls were more popular than SMSs. Stigma was identified as an important barrier to the use of the mobile phone reminders for ART adherence support. The Indian NACP would incur a cost of between 79 and 110 INR (USD 1.27–1.77) per patient per year, based on the type of reminder, the number of patients on ART and the number of ART centres. The total program costs for a scale-up of the mHealth intervention to reach the one million patients by 2017 is estimated to be 0.36% of the total 5-year national-program budget.

**Conclusions:** Despite the positive effect of the intervention on adherence in the cohort, we were unable to detect an effect on time to viral failure and adherence to treatment in the trial. Yet, some participants considered the intervention helpful. The costs of such interventions to national programmes are low. It may be advisable to target specific groups of patients such as those with poor adherence rather than all patients and experiment with different designs of the mHealth intervention.
LIST OF SCIENTIFIC PAPERS


IV. **Rodrigues R**, Poongulali S, Balaji K, Atkins S, Ashorn P, De Costa A. “The phone reminder is important but will others get to know about my illness?” Patient perceptions of an mHealth intervention to support adherence to antiretroviral treatment in South India. (Manuscript)

The papers are referred to in Roman numerals and are called studies in this thesis.
LIST OF ADDITIONAL SCIENTIFIC PAPERS


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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ACTG</td>
<td>AIDS Clinical Trial Group</td>
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<tr>
<td>ART</td>
<td>Antiretroviral Treatment</td>
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<tr>
<td>BLT</td>
<td>Behavior Learning Theory</td>
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<td>CAMPS</td>
<td>Cameroon mobile phone SMS</td>
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<tr>
<td>CD4 T Cells</td>
<td>Type of white blood cell used to monitor HIV progression</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOT</td>
<td>Directly Observed Treatment</td>
</tr>
<tr>
<td>Cumm</td>
<td>Cubic millilitre</td>
</tr>
<tr>
<td>GBP</td>
<td>Great Britain Pound</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Treatment</td>
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<td>HIV</td>
<td>Human Immunodeficiency virus</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>INR</td>
<td>Indian Rupees</td>
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<tr>
<td>IRIS</td>
<td>Immune Reconstitution Inflammatory Syndrome</td>
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<tr>
<td>IRR</td>
<td>Incidence Rate Ratio</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to Treat analysis</td>
</tr>
<tr>
<td>IVR</td>
<td>Interactive Response Voice</td>
</tr>
<tr>
<td>LMIC</td>
<td>Low Middle Income Countries</td>
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<tr>
<td>MEMS</td>
<td>Medication event monitoring systems</td>
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<tr>
<td>mHealth</td>
<td>Mobile Health</td>
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<tr>
<td>ml</td>
<td>Millilitre</td>
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<tr>
<td>MMS</td>
<td>Multi Media System</td>
</tr>
<tr>
<td>NACO</td>
<td>National AIDS Control Organisation</td>
</tr>
<tr>
<td>NACP</td>
<td>National AIDS Control Program</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non Nucleoside Reverse Transcriptase Inhibitors</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitors</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PLWHIV</td>
<td>People living with HIV/AIDS</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>SCT</td>
<td>Social Cognitive Theory</td>
</tr>
<tr>
<td>SMS</td>
<td>Short Messaging System</td>
</tr>
<tr>
<td>SZL</td>
<td>Swaziland Lilangeni</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>USD</td>
<td>US Dollar</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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1 INTRODUCTION

1.1 The global HIV epidemic:

The global prevalence of HIV infection is 0.8% [1]. This translates to approximately 35 million people living with HIV/AIDS (PLWHIV). There is a promising decline in the number of annual new HIV infections and an increase in the global prevalence of HIV infection attributed to effective treatment [1]. The increase in prevalence of HIV infection can also be attributed to the decline in mortality from 2.3 million in 2005 to 1.3 million in 2012 [1].

**Figure 1:** Global distribution HIV infection in adults aged (15-49yrs) [2]

Low and middle income countries, in the regions of Sub-Saharan Africa, South East Asia, South America and Eastern Europe, contribute to 95% of the global burden of HIV infection [1]. Nearly 50% of the global infections are in women. People in the age-group of 15-24 years account for 39% of the infections [1]. Most of the global epidemic is spread heterosexually [3].
In 2012, 63% of the 12.5 million requiring antiretroviral therapy in low and middle income countries received treatment [4]. As per the new WHO treatment guidelines [3], an additional nine million would require treatment in 2013. ART over the years has averted six million deaths globally, 90% of these in low and middle income countries.

1.2 HIV/AIDS:

*The virus:* HIV belongs to the family Lentiviridae. Its genome is made of ribonucleic acid. There are two strains of HIV, HIV-1 and HIV-2. [5]. The predominant strain globally is HIV-1. The infection may be acquired through unprotected sexual intercourse, which is the commonest mode of spread. The other modes of spread are blood transfusions, intravenous drug use that involve unsterilized shared needles and vertical transmission from mother to child. Once in the human body, the virus infects the CD4 cells, macrophages and dendritic cells i.e. the human immune system [6]. It incorporates its genome into the DNA of these cells and replicates, thus destroying the immune system.

At this stage the infection causes flu like symptoms and lymph node enlargement [6, 7]. This is characterised by high viral levels (viral load) in the blood. Subsequent to this, there is an intense immune response and the virus disappears from the blood. This is the “window period.” It may last from three weeks to three months. The appearance of antibodies in the blood heralds the onset of the chronic stage of the disease. Highly sensitive enzyme assays and polymerase chain reactions (PCR) can detect the seroconversion after two to three weeks of infection [3].

The disease is characterized by an acute infection followed by a latent or chronic phase during which the viral load in the blood is low and the CD4 cell count is >500 cells/cumm of blood. Symptoms such as repeated episodes of diarrhea, upper respiratory tract infections, fungal infections, lymph node enlargement and weight loss occur during this stage [7]. The latent stage typically lasts 8-10 years (typical progressors; 80-90% individuals) but may be as short as 3 years (rapid progressors; 5-10%) or may last several years (slow progressors; 5%) [8] During this stage the virus continues to replicate within the immune system destroying it. This is reflected in the declining number of CD4 cells in the blood. Increasing severity of the disease is indicated by opportunistic infections such as tuberculosis and cryptococcal infections, which marks the onset of the acquired immune deficiency syndrome (AIDS) that progresses eventually to premature death [6, 7].
Highly active antiretroviral therapy (HAART) [9]: Over the years, with the development of multidrug treatment called highly active antiretroviral therapy (HAART), HIV has transitioned from a fatal illness to a chronic disease [10, 11]. The drugs developed for treatment are not virucidal and do not provide a cure. They act on the various stages of the HIV life cycle to prevent viral replication in the human body [12]. The commonly used drugs in antiretroviral treatment are: (i) Nucleoside reverse transcriptase inhibitors (NRTI), e.g. Zidovudine (AZT/ZDV), Stavudine (d4T), Lamivudine (3TC). (ii) Non-Nucleoside reverse transcriptase inhibitors, e.g. Nevirapine (NVP), Efavirenz (ENV) and (iii) Protease inhibitors, e.g. Sequinavir (SQV), Ritonavir (RTV), Lopinavir/Ritonavir (LPV), Atazanavir (ATV). HAART, which is a combination of three or more antiretroviral drugs, commonly includes two NRTIs with one NNRTI or protease inhibitor.

Treatment initiation: Traditionally CD4 T cell counts have been used for initiating antiretroviral treatment. Over the years there has been an increase in the recommended CD4 count levels from 200 to 350 and 500 cells/cumm of blood [3]. The rationale for this is that initiating ART at higher CD4 cell levels has been shown to reduce mortality [13].

Markers for disease progression: Traditionally, a fall in CD4 T cell count was considered a good predictor for the development of AIDS [14]. Studies indicate that depletion in CD4 T cells is not a good surrogate for HIV disease progression. Monitoring viral load is the best way to predict disease progression and treatment failure [15]. Viral load, though more expensive to measure, is a direct indicator of treatment failure as it may take several months for CD4 T cells to decline after the onset of treatment failure. A viral load of 1000 copies/cumm of plasma at two consecutive measurements at least one month apart is the criterion for changing treatment in resource limited settings [3]. However, routine viral monitoring is not done in resource limited settings as it is expensive and requires special equipment [16, 17].

1.3 The HIV epidemic in India:

The prevalence of HIV in the India is 0.27% which translates to 2.08 million PLWHIV in the country. Of these approximately 0.7 million are on ART [18]. India has successfully halved the transmission rates of HIV in adults since 2001 [19].

The Indian states of Andhra Pradesh, Karnataka, Tamil Nadu, Maharashtra, Manipur and Nagaland have an HIV prevalence rate that is greater than the national prevalence of 0.27%
Over the years (2000-2011) there has been a 57% decline in the number of new adult infections and a 29% reduction in AIDS related deaths between 2007-2011 [19]. A third of all HIV infections in the country are in women [19]. The HIV prevalence in antenatal attendees, a proxy for the prevalence in the general population, is 0.35% as per the 2013 sentinel survey [20]. India’s epidemic is largely heterosexual (88% of transmission). The other routes of transmission are parent to child (5%), blood products (1%), infected needles and syringes (1.7%) and homosexual (1.5%) [21]. The epidemic in the north-eastern states of Manipur and Nagaland is primarily due to intravenous drug use.

**Figure 2:** HIV High prevalence states in India (prevalence given in percentages)
Table 1: Socio-demography of HIV in India [22] (Overall prevalence 0.27)

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.22</td>
</tr>
<tr>
<td>Male</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>0.34</td>
</tr>
<tr>
<td>Rural</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.32</td>
</tr>
<tr>
<td>Primary</td>
<td>0.43</td>
</tr>
<tr>
<td>Secondary</td>
<td>0.23</td>
</tr>
<tr>
<td>Higher</td>
<td>0.10</td>
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<tr>
<td><strong>Wealth quintiles</strong></td>
<td></td>
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<tr>
<td>Poorest</td>
<td>0.24</td>
</tr>
<tr>
<td>Poorer</td>
<td>0.22</td>
</tr>
<tr>
<td>Middle</td>
<td>0.31</td>
</tr>
<tr>
<td>Richer</td>
<td>0.41</td>
</tr>
<tr>
<td>Richest</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>0.14</td>
</tr>
<tr>
<td>Employed</td>
<td>0.37</td>
</tr>
</tbody>
</table>

1.3.1 A brief comparison of the Indian HIV epidemic with the HIV epidemic in Sub Saharan Africa:

Table 1 gives the distribution of the HIV Epidemic within the Indian population. Unlike the Indian epidemic, the epidemic in sub Saharan Africa is concentrated in females. The epidemic has a more generalized pattern in contrast to the Indian epidemic that is truncated [22, 23]. The mixed association of the epidemic with wealth is seen in both Indian and African contexts. Some argue that the epidemic is economically opportunistic with poverty increasing the chances of infection [23-25]. Others argue that wealth supports risky behavior and maintenance of concurrent multiple partners [23, 26, 27]. The patterns of the epidemic are similar with respect to rural and urban distribution i.e. there is a higher prevalence in urban areas. A higher prevalence in those with lower education is seen in the Indian context unlike in the African context [28].
1.4 MANAGEMENT OF HIV INFECTION IN INDIA:

The first case of HIV infection in India was identified in 1986 [23, 29]. In the year 1992 the National AIDS Control program (NACP) was first launched in India [30]. The program runs in a five-year cycle and is currently in phase IV. The first phase was launched with the objective to control the epidemic. During this period sentinel surveillance was begun and the focus was prevention. The second phase expanded the activities of the phase I. Launched in 2006, phase III aimed to halt and reverse the epidemic. India has managed to successfully reduce the transmission rates of HIV infection during NACP III [31]. Phase IV aims to consolidate the goals achieved, further reduce the rates of HIV infection and meet the Millennium Development Goals [32].

HIV counselling and testing services under the program are provided at integrated counselling and testing centres and antenatal clinics under the NACP at no cost [8].

The entry point for people living with HIV (PLWHIV) into the NACP for care, support and treatment is the ART centre. Patients are initiated on HAART at CD4 cell counts <350 cell/cumm [9]. Presently 0.7 million patients receive ART through 425 ART centres all over the country. These centres provide treatment at no cost to patients through public facilities. Private facilities implement the NACP through public private partnerships [8]. Several link ART centres, have now been established in remote areas, to provide follow-ups and pill refills, however these do not initiate treatment.

ART centres are staffed with a medical officer, a medico-social worker, a nurse, a pharmacist and a data-entry operator. A person diagnosed to have HIV infection can register at ART centres for treatment. They are provided regular follow-ups. Laboratory services such as CD4 cell count assessments are provided biannually. Further, these centres are usually based within larger healthcare facilities that provide referral and inpatient services [33].

Treatment is initiated at an ART centre when the CD4 cell count falls below 350 cells/cumm of blood. The first line regimes for ART involve two NRTIs (zidovudine, stavudine, lamivudine, tenofovir) and one NNRTI e.g. nevirapine or efavirenz. (table 2). Since 2013 stavudine that was used in the first line regime has been replaced by tenofovir [9]. Patients once initiated on treatment visit the ART centre monthly for pill refills. At these visits adherence is monitored. Patients are expected to have a pill count adherence of 90-95% [9]. All patients are counseled, and followed up clinically with laboratory investigations based on NACP recommendations [9].
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Antiretrovirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen 1</td>
<td>Zidovudine+ Lamivudine+ Nevirapine</td>
</tr>
<tr>
<td>Regimen 1(a)</td>
<td>Tenofovir+ Lamivudine+ Efavirenz</td>
</tr>
<tr>
<td>Regimen II</td>
<td>Zidovudine+ Lamivudine+ Efavirenz</td>
</tr>
<tr>
<td>Regimen II (a)</td>
<td>Tenofovir+ Lamivudine+ Efavirenz</td>
</tr>
</tbody>
</table>

Patients are routinely monitored for clinical and immunological failure. Viral load assays are indicated only when clinical or immunological failure is identified. Persistent clinically severe disease for six months after treatment initiation, CD4 T cell counts that fall below baseline, are persistently low or reduce by 50% from their maximum value after treatment initiation and viral loads of >5000 copies/cumm of blood are markers of treatment failure under the NACP. Treatment is however switched only when the viral load crosses 5000 copies/cumm of blood. Further viral load assays are available only at a few designated centres under the NACP to which patients have to be referred if the need arises [34].

First line ART costs the Indian government approximately 5000 INR (85 USD)/patient/year. On the contrary, 2nd line ART costs 6 times that of 1st line treatment and includes protease inhibitors like abacavir, ritonavir and indinavir [34].

Patients who require intensive prolonged care or those without social support may avail such services at community care centres (CCC) supported by the NACP [8].

This entire system of HIV prevention, care, treatment and support is managed at the National level by the National AIDS control organization, Ministry of Health and Family Welfare, and at state level by state AIDS prevention societies. In addition a few centres of excellence for training and research exist [18, 35].

### 1.4.1 The private healthcare sector in India:

The private healthcare sector in India includes charitable organisations, non-governmental organizations, faith-based organisations, corporate hospitals, for profit private clinics and hospitals managed by individuals or a group of healthcare practitioners. Of the urban population, 70% access the private healthcare sector while the same in rural India is 63% [36]. Several of these private clinics/ hospitals also deliver services for HIV care and treatment privately. People are considered to prefer private healthcare facilities due the
privacy afforded by them [37], which is even more relevant in HIV infection, given the associated stigma surrounding the disease. Private healthcare is paid out of pocket by the patient/family. Studies indicate that PLWHIV on treatment could spend up to 50% of their family income on treatment [38], though it is likely that this varies widely.

1.5 mHEALTH:

1.5.1 Mobile phone penetration:
Mobile phone technology has become one of the most pervasive technologies of modern times. There are 6.8 billion mobile phone connections worldwide. Figure 3, shows the global penetration of mobile phones by region [39].

**Figure 3**: Global penetration of mobile phones [15]

This ubiquity of mobile phones has shrunk the world and spurred economic growth and development globally. The technology has penetrated all strata in the population irrespective of socio-economic status. The technology is able to reach remote groups where physical infrastructure is limited and other means of communication are not available. This, coupled with the negligible cost of communication makes mobile phone technology an indispensable convenience. The technology is dynamic, and so are the solutions it provides.
1.5.2 Mobile phones in India

There are approximately 900 million mobile phone subscriptions in India. Urban India has a teledensity that is nearly thrice that of rural India (140 vs. 43 per 100 people) [40]. The monthly growth rate of mobile phone connections is about 0.52% [14]. The costs of mobile phone communication in India are low. A mobile phone handset could cost as little as 10 USD, with a call tariff as low as 0.01 USD/minute. On an average an Indian household could spend as little as 0.036 USD/ capita/month on mobile communication [41]. These low costs have made the technology popular even in the lower socio-economic strata of the Indian society.

1.5.3 The utility of mobile phones for health:

The World Health Organisation has defined mHealth as medical and public health practice supported by mobile technology such as mobile phones, patient monitoring devices, personal digital assistants and other personal monitoring devices [42].

The popularity and ubiquity of mobile phones has been successfully exploited for development [43]. Mobile phones have provided incremental benefits, i.e. improved what people already do by making communication cheaper and quicker [44]. They have provided transformational benefits i.e. newer applications such as m-banking and m-commerce enable consumers to conduct remote transactions [16]. They have not only created employment opportunities, but also created financial opportunities [16].

Mobile phones have provided incremental and transformational benefits within the healthcare sector as well. Quick and inexpensive communications have facilitated management of healthcare emergencies and opened communication channels between patients and the healthcare system [45]. Newer applications for remote monitoring aid the clinical follow-up of patients. mHealth applications also provide support for behavior change, they can be used for remote monitoring and diagnostic support, data collection, healthcare delivery in the community and management of drug supply chain management [45].

Mobile text messaging applications are commonly used to influence behavior change and prevent disease [46]. They are being investigated for increasing awareness in HIV prevention [47, 48]. Medication adherence reminders are used in both communicable and non-communicable disease. The effectiveness of mHealth interventions that target ART adherence both in low-middle and high-income settings is seen in some studies [49, 50]. Few other diseases similarly targeted are hypertension, bronchial asthma and tuberculosis [49, 51-53]. Appointment reminders are shown to successfully improve attendance rates at outpatient.
clinics and vaccination clinics [54]. Text reminders have been found as effective as phone calls and more effective than postal reminders for appointments [54, 55].

Three different combinations of a physician patient interaction via mobile phones for glycemic control is being investigated in Baltimore, USA [56]. These interventions may be simple i.e. that involve just a reminder, or complex that also enable the more complex domiciliary management of disease.

The ‘mobile moms study’ from Australia used SMSs to encourage mothers with young children to exercise [57]. For example, the text4Heart intervention in New-Zealand supports self management in coronary heart disease and involves a combination of messages that address diet, physical activity, smoking cessation, stress management, and illness perception along with treatment adherence [58]. Remote monitoring of blood glucose and management of diabetic care via mobile phones has shown promising results. The intervention designs used text messaging and IVRS in combination with internet technology to communicate with patients and receive reports of home based blood glucose monitoring [59, 60].

Short Messaging Service (SMS) and Interactive Voice Response (IVR) system have been used in smoking cessation programmes in adults and pregnant women in Norway [61]. mHealth interventions have been used to provide information and support to women following medical abortion [62].

The use of SMS technology in mobile phones to communicate laboratory results to HIV-infected patients was found acceptable in Uganda [63]. Telemicroscopic images of pathology captured by approximating the camera lens with that of the microscope and sent to experts using MMS technology were found sufficient for diagnosis by an Italian laboratory [64]. The technology could support diagnosis in settings with sparse healthcare resources and remote laboratories.

Data collection via mobile phones can be real-time and can reduce data fabrication. Data collected via mobile phone questionnaires is quick to upload with minimal data loss and fewer errors compared to data collected on paper [65, 66]. Mobile phones also enable collection of data concerning social interactions and spatial behavior [67]. Such data could be useful in tracking disease outbreaks [68].

Community based health care delivery is effectively supported by mobile communication [69]. Such interventions have been used in the case management of childhood illness and malaria [70-72].
Drug supply chain management is another potential application of mobile phone technology within the healthcare system [73]. Real time monitoring of drug stocks could minimise stock outs at healthcare facilities especially in remote locations.

1.5.4 mHealth in India:
Mobile phones are identified as a tool to enhance capabilities, provide opportunities, enable social networks and improve knowledge within the Indian healthcare system [74]. Further, literature suggests that mobile phones are an acceptable tool for healthcare delivery in the Indian context [75]. The technology was also found acceptable to deliver adherence reminders in the HIV infection [76]. Mobile phones are being used for consultations and fixing healthcare appointments [77].

The government of India is attempting to exploit the ubiquity of mobile phones for healthcare through the Maternal and Child Health Tracking System (MCTS) [78]. This system attempts to generate a databank to support the provision of antenatal, intranatal, postnatal services to the mother, vaccination support to the child and assists healthcare workers with micro planning [78]. The National Rural Health mission also uses mobile phones within its health information system [78]. Indian central government employees receive health care support from the Central Government Health Services Scheme (CGHS) health system via mobile phones. Press releases from the government indicate that mobile phone technology will be used to support nutrition, family planning, drug abuse, non-communicable disease and HIV/AIDS [78].

Information delivered via mobile phones reduced the incidence of diabetes mellitus in those aged 33 to 38 years, at high risk of developing diabetes mellitus in comparison to those who did not in an randomized controlled trial (RCT) in India [79]. Another cluster RCT for the risk management of cardiovascular disease supported with mobile phones is presently underway [80].

1.5.5 mHealth and HIV infection:
HIV infection is perhaps the most common disease targeted with mHealth interventions. Mobile phone applications that address all aspects of HIV prevention i.e. information regarding the disease, HIV testing, condom promotion and safe sex, are available [81] [82, 83]. Preliminary evidence of their efficacy and acceptability is promising [84, 85]. mHealth
platforms for prevention of mother to child transmission were also acceptable to women, their spouses and healthcare workers [48].

Within the HIV management cascade, mHealth interventions most commonly target adherence to ART. The concept transitioned from telephone interventions [86] to mobile phone interventions with the advent of this new technology. One of the first studies with mobile phone reminders for ART adherence demonstrated the potential of the technology to support adherence in a cohort of 8 adolescents who received weekly reminders over 12 weeks [87]. However, it was not until the year 2010 that the results of the earliest large scale RCT from Kenya showed a significant effect of mobile phone reminders on self reported adherence and a weak effect on viral suppression at 12 months [88]. Subsequently, a five-armed RCT, also from Kenya, demonstrated the positive effect of brief messages and weekly reminders in contrast to longer messages and daily reminders on ART adherence [89]. In contrast the Cameroon mobile phone SMS (CAMPS) trial did not show any effect of text messages on ART adherence. However, a pooled analysis of the three studies demonstrated the success of text messaging in improving ART adherence [50]. A study from China showed that mHealth interventions could maintain high levels of ART adherence and affect positively the quality of life of PLWHIV [90].

Retention in care is essential for the success of antiretroviral therapy. Given the lifelong necessity of treatment in HIV infection, discontinuity of care is likely. Ensuring patient retention in care is a responsibility that should be shared by the patient and the health system. Towards this end the ubiquity of mobile phone technology seems to provide an ideal solution, and is currently under investigation for efficacy [91, 92].

Further, communication of laboratory results was acceptable to HIV patients attending an infectious disease clinic in Uganda [63]. The possibility of saving essential resources such as time is an appealing prospect if privacy and confidentiality in such communication is ensured. Communicating HIV related laboratory results especially to remote and rural clinics via mobile phones significantly reduced turnaround time in comparison to providing paper reports in Swaziland [93].
1.5.6 mHealth and privacy:

“Privacy” addresses an individual’s right to control the acquisition and treatment of their recognizable health information or data. On the other hand “confidentiality” refers to commitments towards ensuring privacy of the data obtained [94].

Though mHealth provides a distinctive opportunity to communicate for health, the privacy and confidentiality of such communication has been questioned. mHealth interventions have tried to ensure privacy and confidentiality by making messages neutral, appear as if they are from a friend or disguised to keep the source and receiver confidential [95]. This is of particular concern when mHealth interventions target HIV infection as they have the potential to cause stigma from unintended disclosure of the HIV status [96].

Further, health information obtained via mobile phones is subject to the same ethical guidelines as any other means of data collection. However, unlike paper based healthcare records, cyber networks are difficult to secure. Hence a need for innovative strategies for protection of cyber data is a requirement.

1.6 ADHERENCE TO MEDICATION

1.6.1 Adherence and behavior:

The burden of chronic disease is increasing globally. Chronic diseases require long-term treatment for a healthy life. However, for successful health, clinical and quality of life outcomes it is necessary for patients to take medications as prescribed. This “act of taking medications as prescribed” was called “compliance to medication” [97]. Factors, both extrinsic and intrinsic to the patient govern medication-taking behavior. This understanding of the multi-factorial nature of medication taking behavior and the role of the patient led to a new concept called “adherence to medication” [98]. Adherence in contrast to compliance recognizes the conjoined responsibility of the patient and the physician in ensuring health.

Adherence is multidimensional and complex and so are its determinants [99]. It has been considered an outcome of five dimensions [100] that include (i) socio-economic factors i.e. age, education, poverty, social support, (ii) the therapy i.e. the medication regimen, dose, schedule, number of pills, side effects (iii) the healthcare system i.e. availability of medications, prescribing practices, physicians knowledge regarding management and costs of distribution (iv) the health condition i.e. acute or chronic, infectious or non-infectious
disease, co-morbidities and (v) patient related factors such as the patients’ knowledge regarding the illness, attitude towards the disease, beliefs regarding treatment, perceptions of severity of the disease and self-efficacy for adherence.

1.6.2 HIV and medication adherence:
Factors for non-adherence to ART are similar to those in other chronic disease. In HIV, regimens with single pills, female sex, those with a better quality of life are associated with optimal adherence [101]. On the other hand, unprotected sexual intercourse and substance abuse are associated with sub-optimal adherence [101]. Studies also indicate that self-efficacy, beliefs regarding medications, trust in the healthcare provider and social support were strongly associated with optimal adherence [102].

Unlike most diseases, adherence in HIV infection is a challenge due to additional factors such as the nature of disease transmission, the prognosis of HIV without treatment and the stigma that surrounds HIV [102, 103]. While these factors can make an individual more adherent to medication, they can also lead to sub-optimal adherence [5].

Studies from the Indian context indicate that the proportions of patients adherent to ART vary from 50%-97% [104-107]. Proportions of patients reporting treatment interruptions ranged between 20-33% in different studies [104, 108].

Barriers to ART adherence in the in the Indian context [104, 105] are comparable with those in other contexts [5]. Social barriers such as nondisclosure of HIV status, social support are seen in some studies [109]. Health system related barriers include long waiting times at clinics, long travel time to ART centres and costs of treatment [110, 111]. Forgetfulness is a common barrier reported in the Indian context. It is reported as just simply forgetting to take the medication, busy with other things or being away from home [106] [107]. A study from north east India reported forgetfulness in 11% of the respondents; similar reports are available from other studies in the Indian context [107, 110, 112].

1.6.3 Measuring adherence:
Adherence may be measured using patient self-reports, pill counts, medication refill rates, medication event monitoring systems and biomarkers or therapeutic drug monitoring [113].
Though patient self-reports are the simplest ways to measure adherence, they are subject to a strong social desirability bias. They are also influenced by recall. Therefore they may be unreliable despite proven validity. The four-day recall [114], the visual analogue scale [115], the Morisky scale [116], medication adherence rating scale [117], ASK-20 [118] are some methods of assessing self reported adherence [113].

**Pill counts [119, 120]:** These assess the numbers of pills returned based on those prescribed to be taken at the previous visit. It is calculated as a percentage. While pill counts are objective in comparison to self-reports, they are also prone to social desirability bias. Pill counts are also known to overestimate adherence due to pill sharing, pill dumping or lost pills. Patients may either forget to return their pills or chose not to return them in an attempt to conceal their true adherence. Some patients might find pill counts intrusive.

**Pharmacy refill rates [121]:** This is an unobtrusive method of assessing patient adherence without the patient’s knowledge. It reflects the patient’s intent to continue the prescribed medication voluntarily. It provides the frequency of pill refills over time and numbers of pills bought to provide an adherence rate over time. It may not be feasible in healthcare settings that do not use a closed pharmacy circuit or if pharmacy records are poorly maintained.

**Biomarkers and therapeutic drug monitoring [113]:** These are assays of body fluids or tissues that study the concentrations of the drug or its metabolites to indicate if the patient is adherent. These assays are feasible if the medications have a long half-life. Hair assays for antiretroviral drugs [122] and urine dip stick tests for isoniazid [123] seem to show promising results. These assays may be valid within specific periods of time or may be biased if the patient takes the medication just prior to the assay to appear adherent [124].

While TDM is feasible for monitoring antiepileptic and anti-arrhythmic drugs, they are not as effective in monitoring ART adherence. The feasibility of TDM for ART monitoring is limited by its cost and inter-individual variability making standardization of the assessments difficult [125]. Inter-individual variability in drug concentrations is attributed to drug differences in solubility and absorption from the intestine. Further the drugs cannot be pushed to maximum doses due to absorption and tolerability limitations. Hence, therapeutic ranges are difficult to evaluate [37, 125]. The concentration dose relationship for NNRTIs is not well established, making it difficult to predict the dose response. Accurate reporting of when the last dose is a necessity for accurate assessments [125]. Given this complexity and uncertainty in TDM for ART, and its costs it is not considered a feasible option for monitoring ART adherence.
Medication event monitoring systems (MEMS): First developed by Eisen et al and improvised by the Apex Corporations, it is considered as the gold standard for adherence assessment [124, 126]. The technology comprises of a computer chip embedded in the cap of a medication bottle. It records data related to frequency and time at which the bottle was opened but does not indicate who opened the bottle or if the pills were actually taken. It may therefore be subject to social desirability bias or erroneous recordings.

1.6.4 Measurement of adherence to antiretroviral treatment:

For treatment success patients should have at least 95% adherence to treatment with objective adherence assessments such as the pill count (percentage of pills taken of those prescribed) [127]. These high levels of adherence are necessary to suppress the levels of the virus to <400 copies/cumm [127]. Recent studies indicate that with NNRTI based regimens lower levels of adherence (measured by pill count) may be sufficient to maintain viral suppression [128]. However, higher levels of adherence means better disease prognosis [128]. Further, poor adherence leads to development of drug resistance requiring a change in treatment regimens [129-131].

Methods used for assessment of adherence to antiretroviral therapy are self reports such as 4-day recalls and visual analogue scale, the pill count and the MEMS [132].

Most research studies use an adherence cut-off of 100% with patient self-reports to define optimal adherence, while the cut off is 95% for relatively more objective measures such as the pill count [132]. These cutoffs reflect the correlation with viral load that best predicts disease prognosis. Though these assessments are derived from studies with protease inhibitors, they have been used in the scientific literature to define adherence even with NRTIs and NNRTIs.

1.6.5 Health behavior models and adherence to medication:

Several behavioral theories have been adapted to explain medication adherence behavior. Beliefs and attitudes play an important role in preventing disease and ensuring health. Hence most behavioral theories are centered on patient’s knowledge attitudes and beliefs [99]. The health belief model, the theory of reasoned action, the information motivation strategy, the social cognitive theory (SCT) and the behavior learning theory (BLT) are some models that have helped theorise and develop healthcare interventions [99]. The SCT reflects the Indian
HIV care and management system while the BLT provides a theoretical model for the mHealth intervention studied in this thesis.

*Social cognitive Theory [99]:* This model suggests the influence of personal and environmental factors on behavior. Modifying either could bring about the desired change in behavior. The theory also considers the influence of past experience in directing a desired action. An action that brings about a desired positive outcome may be sustained while one that brings about an undesired outcome may be modified. Similarly positive environmental influences, stimuli like praise or reward can sustain a positive change and vice versa. However what drives this theory is self-efficacy. The individual believes in their ability to bring about the desired change. The theory can effectively explain change in adherence behavior. This model has been used to describe the adherence support provided through the NACP. Under the NACP, participants are assessed for their knowledge of the disease and gaps are addressed. Barriers to adherence are identified and addressed along with enabling patients to identify routine external cues that may be used for adherence support. In doing so adherence counselling also promotes the development of a sense of self-efficacy in the patient [133].

*Behavior Learning theory [99]:* The behavior learning theory (figure 4) proposes the presence of antecedents which may be internal i.e. thoughts that inform an individual that the medication has to be taken or external i.e. cues that remind the patient to take their medications (medication reminder systems). The result of these antecedents is an action i.e. taking of medicines and a consequence i.e. wellbeing or ill health, medication side-effects. The consequences may be viewed as either a reward or punishment. Sustaining the behavior is largely dependent on consequences that reinforce antecedents. The mHealth reminder intervention can be posited within this theory as an external cue to medication adherence.
Figure 4: The Behavior learning theory framework

Internal antecedents: Thoughts that direct adherence behavior

External cues: Medication reminder systems

Behavior
Taking medicines

Consequences
Wellbeing
Side effects
Ill health
2 OVERALL AIM

2.1 AIM:
This thesis designed and tested a mhealth intervention to improve adherence to antiretroviral therapy (ART) in HIV patients in South India. Further perceptions regarding the intervention and costs of the intervention from the perspective of the national program were also studied.

2.1.1 Objectives
Study I: To assess the effectiveness of an mHealth reminder on adherence to ART in a cohort of patients already on treatment.

Study II: To assess the effectiveness of an mHealth reminder on ART adherence in ART naïve patients in an RCT (HIVIND RCT).

Study III: To assess participant perceptions regarding the mHealth intervention used in the HIVIND RCT.

Study IV: To assess costs of the mHealth intervention used in HIVIND RCT from the perspective of the Indian National AIDS Control Program.
3 CONCEPTUAL FRAMEWORK

The conceptual framework used in this thesis is one that I have developed based on a combination of the frameworks by Gellad FW et al (2009) [134] for adherence and Coomes CM et al (2011) [135] for supporting adherence with SMS technology. The framework (figure 4) I have developed has 4 primary components, (i) the individual or patient factors placed at the centre of framework, stressing the necessity of a patient centered approach to any healthcare intervention, (ii) the intervention and (iii) adherence behavior and (iv) the outcome.

Figure 5 pictorially describes the conceptual framework and shows how the different studies in this thesis are positioned within the framework.

**Figure 5:** Conceptual framework for mHealth ART support [Ref: Gellad FW et al (2009) and Cooms et al (2007)]
3.1 COMPONENTS OF THE FRAMEWORK:

(Figure 5)

**The intervention:** *External cues*: Cues may be internal or external. *Internal* cues occur when the intention to carry out an activity reaches a level at which it “pops into the mind” spontaneously [136]. In other words the patient is reminded of the medication automatically without the need for an external stimulus. *External cues* are stimuli or triggers [136] from outside, such as a note in a diary or an alarm that reminds the individual of the intention to carry out the activity. mHealth interventions are considered external cues to medication adherence.

While designing an mHealth intervention, the following aspects must be taken into consideration [135]: (i) single or multiple components i.e. combination of SMS and voice calls or multiple components within an SMS or voice call based intervention (ii) engagement or interactivity in the communication (iii) Timing most suitable to receive the call (iv) frequency i.e. once/twice daily or weekly. This may be based on the purpose of the intervention i.e. medication reminders or appointment reminders or providing information. Literature cautions that repetitive and weak stimuli cause in “habituation” or “fatigue” i.e. a lesser desired response [137] (v) tailoring i.e. the content of the message may be personalized to the individual, the disease or health status and the objective of the intervention. Additionally the frequency and interactivity of the intervention may also be tailored to the patients need.

**The patient:** There are a number of elements that influence patient behavior. From an individual standpoint, *cognitive function* i.e. memory, is the primary target of mHealth reminder systems. Patients/ beneficiaries may choose to pair this reminder with another cue, to minimize forgetfulness, a commonly reported factor for medication non-adherence.

Adherence is influenced by the patients’ demography i.e. age, education, etc. Additionally, the patient’s perceptions regarding the illness, co-morbidities, medication characteristics such as dosing and pill burden also influence adherence and patient behavior. The patient lives in a family that is a unit within a community, both of which provide social support. The patients, along with their social support system, are within the health system. Hence, healthcare access and coverage, costs of care, medication-supply and doctor patient relationships influence adherence.
**Adherence behavior:** The behavior induced by the external cues is medication adherence. The principle of operant conditioning can be used to explain such behavior. The stimulus i.e. reminder, induces the patient to take the medication.

**Outcomes:** Better health and quality of life are “positive reinforcers” of good adherence behavior. In lay terms this is called a “reward”, which increases and sustains the adherence behavior.
4 METHODS

This thesis uses quantitative and qualitative approaches, different epidemiological study designs, data collection tools and analytical approaches best suited to address each research question concerned. These are summarized in table 3.

Table 3: Study matrix

<table>
<thead>
<tr>
<th>Study</th>
<th>Research Question</th>
<th>Design and sample</th>
<th>Setting (Country: India)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Is the implementation of a periodic mobile phone based adherence reminder intervention in a cohort of PLWHIV on treatment feasible?</td>
<td>Quasi experimental design over one year Patients received the intervention for the 1st 6 months only. Sample size: 150</td>
<td>St. John’s Medical College, Bangalore</td>
<td>Change in adherence over time</td>
</tr>
<tr>
<td>II</td>
<td>Will an mHealth reminder intervention influence adherence in PLWHIV on treatment in comparison to those who do not receive the intervention?</td>
<td>Randomised controlled trial over 3 years Sample size: 631</td>
<td>• St. John’s Medical College, Bangalore, Karnataka • KR Hospital Mysore, Karnataka (323 subjects) • YRG Care Chennai, Tamil Nadu (310 subjects)</td>
<td>Time to failure, change in adherence over time between the two arms</td>
</tr>
<tr>
<td>III</td>
<td>What are the experiences and concerns of participants in the intervention arm of sub Study II regarding the mobile phone reminder interventions?</td>
<td>In depth interviews with intervention arm participants after study 2 Sample size: 16 patients</td>
<td>• St. John’s Medical College, Bangalore. (5 patients) • KR Hospital, Mysore, Karnataka (5 patients) • YRG Care Chennai, Tamil Nadu (6 patients)</td>
<td>Participants’ experiences regarding the infection</td>
</tr>
<tr>
<td>IV</td>
<td>What is the cost for scale up of an mHealth adherence support intervention?</td>
<td>Micro-costing of the intervention in Study II</td>
<td>• St. John’s Medical College, Bangalore, Karnataka • YRG Care Chennai, Tamil Nadu</td>
<td>Costs of the intervention and its components</td>
</tr>
</tbody>
</table>
4.1 STUDY CONTEXT:

The study was based in South India (figure 6). The region has 3 of the HIV high prevalence states, i.e. Karnataka, Andhra Pradesh and Tamil Nadu. The study centres were located in Karnataka and Tamil Nadu and were in close proximity to Andhra Pradesh.

Figure 6: Map of India showing the HIV high prevalence States and the study centres
Karnataka has a population of 61 million and an HIV prevalence rate of 0.52%. Two of the study centres were located in Karnataka. Kannada is the official language in the state. The political capital of the state is Bangalore. This city is India’s “IT hub”. The city has a population of nine million. Migration into the city from different parts of the country due to the employment opportunities generated by the IT industry has led to a cultural and ethnographic mix in the city’s population. Our second site in Karnataka was in the city of Mysore, south of Bangalore, with a population of 3 million.

Tamil Nadu has a population of 72 million and an adult HIV prevalence rate of approximately 0.28%, which is close to the national average of 0.27%. The population in the state is predominantly Tamil speaking. This language is also the official language in the state. Our second study centre was located in Chennai, the political capital of Tamil Nadu.

4.2 STUDY CENTRES:

St. John’s Medical College Hospital: This hospital located in Bangalore city was one of the three study centres. It is a private, faith based, tertiary level teaching healthcare facility. The hospital has an outpatient ART treatment centre that implements the NACP in a public private collaboration with the NACP. There are approximately 3000 PLWHIV registered at the ART centre in this hospital for treatment and follow-up. Of these 2000 PLWHIV are currently on treatment.

Krishna Rajendra Hospital, Mysore: is a public tertiary level teaching facility. This facility has approximately 10000 PLWHIV registered for care and treatment under the NACP, of these 5000 are currently on ART. The hospital provides inpatient and outpatient treatment at no cost to patients. Mysore is approximately 150 Kilometers from Bangalore and can be reached in approximately 3-4 hours by road or the train.

YR Gaitonde Centre for AIDS research: This hospital, based in Chennai, Tamil Nadu, was the 3rd study site. This is a private, not-for profit healthcare facility. It provides care and support to PLWHIV at minimal costs. Its services include inpatient and outpatient care through an 18-bedded inpatient facility, HIV related counseling and testing services, treatment, follow-up and peer support. One of its primary aims is HIV related research. Approximately 17000 PLWHIV avail care, treatment and follow-up services at this centre.

Standard care at these centers: A team that includes doctors, nurses, counselors, outreach workers and data entry operators deliver care and treatment to PLWHIV at each of these
centres. Subsequent to diagnosis patients register at ART centres for treatment and follow-up. Pre ART follow-up includes biannual clinical and immunologic monitoring (CD4 count assessments) and outpatient care as necessary. ART is initiated when the CD4 count drops below 350 cells/cumm or with increasing clinical severity of the illness. Patients initiated on treatment are monitored monthly for adherence to ART, clinical follow-up and immunologic progression monthly. They also receive laboratory investigations when necessary e.g. CD4 count assessments, hemoglobin estimation, etc. Patients receive counseling at treatment initiation and follow-ups.

Patients return monthly for pill refills. At these visits a nurse assesses their adherence to ART using the pill count method. This is followed by adherence counseling by a medico-social worker.

*Pre-ART adherence counseling [9]*: Subsequent to assessing the patients knowledge regarding HIV infection, attempts are made to clear misconceptions regarding the disease. The patient is educated based on the gaps in knowledge identified. Counseling includes discussing the realistic potential of the treatment for cure and prevention of transmission, planning of and the need for regular follow-ups, diet, identifying barriers to adherence, potential solutions and finances.

*Follow-up counseling [9]*: Participants visit the centre monthly for pill refills. At these visits pill count assessments are made prior to dispensing pills. The nurse or pharmacist makes these assessments. The patient then receives counseling from a designated counselor. The content of counseling includes the names and schedules of medication, diet in relation to medication, adherence related issues, identifying and reporting side effects. In doing so, counseling promotes the development of a sense of self-efficacy towards medication adherence in the patient.

### 4.3 THE INTERVENTION

Prior to designing the intervention a survey was conducted to understand patient preferences regarding the type, frequency and acceptability of a reminder to support ART. The study indicated that 73% of the patients owned a mobile phone. Most participants (80%) preferred voice call reminders and 60% were open to receiving SMS reminders. Participants also preferred receiving the reminders weekly once [107]. Based on this feedback we developed a multiple component reminder for ART adherence support.
Components: This was an automated multiple component intervention. It comprised an IVR call [138] and a pictorial SMS reminder, each sent out once a week, three days apart. A participant chosen to receive the intervention received both components of the intervention.

The IVR call: The call said, “Hello, this is your good friend calling you! If you have taken all your medications yesterday please press “1” if no please press “2”.” If the patient missed the first call, three additional calls were attempted in the next 24 hours.

Frequency: The call was made to the patient once a week.

Personalization and Timing: Participants could choose one of five languages for the call, i.e. Hindi, Kannada, Tamil, Telugu or English. We matched the sex of the voice for the call i.e. male or female with that of the patients. They could also choose a day and time for receiving the IVR. The number from which the call was received was saved under a name the patient chose in their mobile phone’s directory. Participants receiving the intervention were trained to receive and respond to the voice calls.

SMS reminder (figure 7): This was a pictorial SMS that depicted a “lamp”. The SMS was also sent to the patient once a week, usually three days after the IVR call. The SMS was personalized to the time that the patient chose to receive it.

Figure 7: The pictorial SMS

All study participants were given a mobile phone irrespective of owning one and irrespective of their allocation in trial.
4.4 STUDY 1: EFFECT OF AN MHEALTH INTERVENTION IN A COHORT

Objective: To assess the effectiveness of an mHealth reminder on ART adherence in a cohort of patients already on treatment.

Methods:

Study centre: This study was based at St. John’s Medical College Hospital only.

This was a quasi-experimental study in a cohort of 150 PLWHIV on treatment. The overall duration of the study was one year. The study was done in two phases, (i) Intervention phase lasting six months during which the participants received the intervention along with standard care and (ii) a follow-up phase lasting 6 months more during which the intervention was stopped, but routine standard care continued.

Inclusion criteria: PLWHA attending the ART centre were eligible to participate in the study if they had access to a mobile phone with network coverage at their residence and were willing to attend all study visits. However, PLWHIV who were seriously ill, or those that had a participant in their family were excluded.

Data collection: Participants were followed up one month, three months, six months, nine months and 12 months from recruitment. At these visits adherence to ART was assessed using the pill count. Participants’ perceptions regarding the intervention were also assessed at six months i.e. on completion of the intervention phase of the study. All data was collected by trained research assistants.

Outcomes assessed:

Adherence to treatment: The primary outcome assessed was change in adherence over time. Adherence was measured using the pill count. Using this method adherence was calculated as

\[
\text{Number of pills the participant should have taken} - \text{Number of pills actually missed} \times 100 \\
\text{Total number of pills the participant should have taken}
\]

Optimal adherence was defined as an adherence level of \( \geq 95\% \). Adherence was assessed at each follow-up visit. Barriers to adherence were also assessed at each follow-up visit during the intervention with the AIDS Clinical Trial Group barriers to adherence self report instrument (ACTG q10777).
Perceptions regarding the intervention: This was a quantitative questionnaire based assessment of participants’ perceptions regarding the intervention in the cohort. Trained research assistants interviewed participants at the end of the intervention phase to assess the different facets of the intervention like, intervention receipt, usefulness, privacy and intrusion. The responses were recorded on a 5-point Likert scale.

Analysis:

Change in adherence over time was compared using the Cochran’s Q. The data was then subjected to the Mc Nemar’s test to identify which two time points contributed to the overall significance. Binary logistic regression models were used to identify demographic and clinical predictors of adherence at baseline.

In order to ensure a robust analysis of change in adherence over time, a sensitivity analysis of adherence was done wherein missing data was treated as follows: (i) Complete case analysis, i.e. missing data excluded from the analysis (ii) missing = non adherent (iii) missing = adherent.

STUDY II, II, IV:

The HIVIND was a randomized controlled trial designed to test effectiveness of the mHealth intervention on treatment outcomes. Studies III and IV were nested within the HIVIND RCT and assessed participant perceptions with the mHealth intervention qualitatively and the costs of the intervention.

4.5 STUDY II: EFFECT OF THE mHEALTH INTERVENTION IN A RCT (THE HIVIND RCT)

Objective: To assess the effectiveness of an mHealth reminder on ART adherence in ART naïve patients in an RCT.

Methods:

Study centers: The study was implemented at Bangalore, Mysore and Chennai, over a period of 3 years from August 2010 to August 2013.

Inclusion criteria: PLWHA attending the ART centre were eligible to participate in the study if they were ART naïve, resided in one of four South Indian states i.e. Karnataka, Tamil
Nadu, Andhra Pradesh and Kerala, had mobile network coverage at their residence and were willing to attend all study visits over two years.

Exclusion criteria: Those PLWHIV who were seriously ill, were found positive for HIV-2 virus, those that had a study participant in their family, were excluded from the study.

Eligible participants were administered written informed consent, after which they were provided detailed information on the study, its purpose and requirements.

**Study design:** This was a randomized controlled trial that tested the mHealth intervention for effectiveness in 631 ART naïve PLWHIV initiating treatment (Figure 8). PLWHIV initiating treatment were screened for eligibility and enrolled in the study subsequent to written informed consent. The expected duration in the study per participant was 96 weeks.

**Figure 8:** The HIVIND RCT

Randomisation Procedure: Patients were randomized in permuted unequal blocks of 4 and 6 subsequent to sex stratification with an allocation ratio of 1:1. Sequentially numbered opaque sealed envelopes were used to conceal randomization. Subsequent to enrolling a patient an envelope was opened in serial order based on the patient’s sex, and the patient allocated to the arm indicated. Patients who were allocated to the intervention arm were trained to receive and respond to the intervention.
Sample size: The sample size necessary for the study was calculated based on an alpha of 0.5, a hazard ratio of 0.75 and a power of 90% using STATA 10 software. The sample size obtained was 258. This was inflated by 10% (283) to account for loss to follow-up and rounded off to the nearest 100 to give a sample size of 300 per arm.

Overall, 631 patients were randomized to either receive the intervention or only standard care.

Follow-up and Outcome assessed:

All patients received standard care. However, those in the intervention arm received the intervention along with standard care. All patients enrolled were given a mobile phone and monthly call credit.

Follow-up: All patients were followed up every three months for 96 weeks or till they reached primary end-point whichever earlier. Primary end point: Viral failure, defined as 400 viral RNA copies/ml, at least one month apart, six months or more after initiation of ART. Loss to follow-up and death were considered as secondary end points.

Outcome: Primary: Time to viral failure was the primary outcome based on the viral failure as indicated by viral load assessments. Secondary: Proportion adherent to ART. This was assessed and defined as in Study I.

Analysis:

Primary outcome: The primary outcome was compared in the intervention and control groups in an intention-to-treat analysis. Time to viral treatment failure, was compared between the two arms using Kaplan Meir survival analysis. The cox proportional hazards model was used to identify demographic and clinical factors associated with time to viral failure. Rates of retention and death were also compared between both the arms.

Secondary outcome: Adherence to ART was assessed as in Study I and compared between both arms. Poisson regression was used and incidence rate ratios (IRR) calculated by dichotomizing the mean adherence rate per person.
4.6 STUDY III: PERCEPTIONS OF THE PARTICIPANTS REGARDING THE mHEALTH INTERVENTION

Objective: To assess participant perceptions regarding the mHealth intervention used in study II.

Methods:

Study setting: The study was nested within the HIVIND trial. It therefore included participants from all the three study centers, i.e. Bangalore, Mysore and Chennai.

Study design: This was a qualitative study that used in-depth interviews to assess participant perceptions with the mHealth intervention.

Data collection: Participant experiences with the intervention in the HIVIND trial were studied through in-depth interview at all the three study centres. Overall 16 participants in the intervention arm who had completed at least 84 weeks in the study were interviewed. Participants were purposefully selected to represent different age and sex strata, occupations, residence areas and socioeconomic subgroups.

For the interviews, I prepared an interview guide with the following the domains (i) helpfulness of the intervention (ii) frequency of the intervention (iii) ease of use (iv) issues faced with receiving and responding to the intervention and (v) intrusion as a result of the intervention. I conducted the interviews at the Bangalore and Mysore centers. At Chennai, research assistants trained in in-depth interviewing conducted the interviews in my presence. All interviews were conducted away from the ART clinic. All interviews were audio recorded subsequent to obtaining written informed consent from the patient. The recordings were delinked from patient's demographic details in order to ensure anonymity.

Analysis

We used the Framework approach to qualitative data analysis by Ritchie and Spencer (2004). All interviews were transcribed and translated into English by a native Kannada or Tamil language speaker also fluent in English. These translations were subsequently spot checked with the recordings to ensure that they matched. I then familiarized myself with the first few interviews and identified codes in the data. The codes were used to develop the analytical framework that was entered into an MS excel spreadsheet. The analytical framework developed was then applied to the rest of the transcripts i.e. the transcripts were indexed.
Additional codes were generated and included in the framework as the analysis progressed. Text from the transcripts that matched the codes was then charted into the framework created. The charted verbatim accounts were subsequently summarised. The text was then labeled to ensure that it could be traced back to the transcript. Connections between the codes were then mapped to explore relationships between them. This led to identification of sub-themes. Sub-themes were further grouped together to derive themes from the data.

4.7 STUDY IV: COSTS OF THE mHEALTH INTERVENTION

Objective: To assess costs of the mHealth intervention used in HIVIND RCT from the perspective of the Indian National AIDS Control Program.

Methods

Study centers: The study was conducted at St. John’s Medical College Hospital, Bangalore and KR Hospital, Karnataka, India.

Study design: This was a costing study that used a micro-costing approach i.e. collecting data per unit of the item/commodity consumed.

Costs:

One time costs: These were costs incurred only once in the trial, these primarily included costs for intervention development.

Recurrent costs: These were costs incurred every year. They included fixed and variable costs. Fixed costs were those that did not change based on the volume of output. Variable costs fluctuated with the volume of output e.g. number of patients receiving the intervention.

Costs from the perspective of the national program and scale-up of the intervention

Costs at National Program level: These were (i) one time costs for equipment, intervention development, and communication with ART centres under the program for the purpose of the intervention (ii) recurrent fixed costs for a program manager and costs for maintenance of the internet web interface that sent out the intervention to capture patient responses and other data regarding the intervention.
Costs at ART centre level: These included one time costs for equipment like a laptop and computer and recurrent fixed costs for the intervention like (i) 10% time of personnel involved in program management and data management (ii) overheads, i.e. 10% of costs incurred for running the ART centre annually.

Patient level: These were primarily variable costs and included (i) costs per IVR call and SMS and (ii) Counsellors time. These costs were derived from dairies maintained by the counsellors. On an average, one hour per patient per year for training the patient to receive and respond the intervention and following up intervention receipt with the patient. These costs varied based on the number of patients receiving the intervention.

Outcome assessed:

Annual costs of the intervention for each component i.e. IVR only, SMS only and IVR and SMS combined were assessed. Annual costs of scale up of the intervention to national level from the perspective of the NACP.

Analysis:

Total costs per year for deployment of the mHealth intervention: These were calculated as a function of fixed and variable costs using the formula: Total cost for deployment of the (IVR call plus SMS) = Program level cost + (number of centres x centre level cost) + (n x patient level cost); where n = the number of patients.

Total costs for each component of the intervention were calculated with the same formula, however costs contributed to by only that component of the intervention were considered. i.e. IVR or SMS.

Costs per patient per year: These were calculated by dividing the total costs per year for deployment of the mHealth intervention by the number of patients expected to receive the intervention during that year.

Sensitivity analysis based on estimates of the number of ART centres, patients on treatment and the components of the intervention

Sensitivity analysis: Sensitivity analysis was done by varying (a) the number of patients and the number of ART centres (b) the type of mHealth intervention deployed, i.e. (i) only IVR, (ii) only SMS or (iii) both SMS and IVR used in combination.
Estimates of expected PLWHA numbers under India’s NACP in 2017 were obtained from three different sources (i) a published mathematical model which estimated 500,000 patients on ART in 2017 [139] (ii) Planning Commission, Government of India estimate of 800,000 patients on ART in 2017 [140] (iii) National AIDS Control Organisation (NACO) estimates for 100,000 patients on ART in 2017 [141, 142].

4.8 ETHICS:
Written informed consent was obtained from participants for Study I, II and III for participation in the studies. In addition, written informed consent for audio recording was obtained for participants in study IV.

Ethical approvals for the studies were obtained from the respective ethics committees at each of the study centres; (i) St. John’s Medical College Hospital, Bangalore: IERB 1/369/08 – 92/2008 (All studies) (ii) Mysore Medical College and Research Institute: NO/PS/173/2010 (Studies II, III and IV) (iii) YRGCare Medical Centre, Chennai: IRB April18/2009 (Studies II and IV)
5 RESULTS

5.1 STUDY I: mHEALTH INTERVENTION IN A COHORT

Overall 150 patients were enrolled in the study and followed up for a period of 1 year. Most of the participants were male, 109 (73%), lived in an urban area 135 (90%). They were either on a Zidovudine or a Stavudine based regimen. Literacy rate was significantly associated with baseline adherence (p<0.027). They were on treatment for 18-28 months at enrolment in the study.

Nine (6%) of the 150 participants had missing adherence data at different time points. Of these nine participants, three were transferred out to another clinic for second line ART, four were transferred to clinics closer to their homes for logistic reasons and two could not be traced.

Complete case analysis for 141 participants with complete data showed that there was a significant improvement in proportions adherent over time (p = 0.016) (Fig. 6). Similarly when missing adherence data at any time point was considered ‘adequately adherent’ a significant increase in proportions adequately adherent over time was seen (p = 0.022). However, when missing adherence data at any time point was considered as ‘not adequately adherent’, no significant increase in proportions adequately adherent over time was seen (p = 0.321) (Figure 9).

**Figure 9:** Adherence trends based on the type of analysis
The most common reason for missing medications throughout the study was forgetfulness, which reduced significantly with time 17%; 10%; 6% and 3% at baseline, 1 month, 3 months, and 6 months respectively, p<0.001).

Of the 136 participants who responded to the survey on the perceptions, 60 (44%) preferred both the phone call and the SMS, 42 (34%), preferred only the phone call, 15 (11%) preferred only the SMS, the rest did not like the intervention at all.

5.2 STUDY II: EFFECT OF THE mHEALTH INTERVENTION IN AN RCT (HIVIND TRIAL)

Demographic profile of the participants: Of the 1140 PLWA who were screened, 631 were enrolled in the HIVIND RCT. Of these 315 were randomized to receive the intervention. A description of the recruitment and retention of participants in the trial is given in figure 10. There were 157 participants enrolled at Bangalore, 164 at the Mysore and 309 at Chennai. Of those enrolled 243 (43%) were female, 129 (20%) were not literate and 233 (37%) were unemployed. Five hundred and twenty three (83%) participants were familiar with using a mobile phone. Clinically, 245 (54%) of the participants had stage 3 or 4 disease and 25 had baseline drug resistance. At recruitment, 523 (83%) had ever used a mobile phone while, 175 (28%) shared a mobile phone. There was no significant difference in the distribution of demographic variables in the two groups at baseline. The demographic details are described in manuscript for Study II.
Figure 10: Flow chart of patient recruitment and retention in the trial

HIV-1-infected ART-naïve individuals, about to start ART assessed for study eligibility

1140

Excluded 509
Not meeting inclusion criteria 358
1 Age <18yrs or >60 years (74)
2 Severely ill (115)
3 Participant in same household (17)
4 No phone network (1)
5 Not interested (151)
Declined to participate: 139
Other reasons: 12

Randomized

Allocated to and received mobile phone intervention: 315
Allocated to and received standard care: 316

Died 21
Lost to follow-up 12
Withdrew consent 12

Died 23
Lost to follow-up 21
Withdrew consent 9

Included in primary analysis 315
Included in primary analysis 316
**Primary outcome:** There was no significant difference in the time to survival between the intervention and control groups (adjusted HR 0.96, 95% CI 0.64-1.43) (Figure 11)

**Figure 11:** Proportion of people experiencing viral failure over time

![Proportion experiencing failure over time in each arm](image)

**Secondary outcome:** Proportion adherent to ART

There was no significant difference in the incidence rate ratio of those optimally adherent between the two groups over time (adjusted IRR 1.24, 95% CI 0.94 -1.63).

**Fidelity of the intervention:** There were 316 patients randomized to receive the intervention during the study. They contributed 24227 patient weeks in the study during which 23070 calls were made to these participants. Similarly, 23806 SMSs were sent to the participants, of which 65% were actually delivered.
Reasons for not receiving the intervention: Being away from the phone, poor network connectivity, lost phones and changing the phone number were reasons reported for not receiving the calls. Difficulty in accessing the SMS was an additional reason reported for not viewing the SMS.

5.3 STUDY III: PERCEPTIONS REGARDING THE mHEALTH INTERVENTION

Of the participants in the HIVIND RCT 16 were chosen for the qualitative study. There were five participants each at the Bangalore and Mysore centres and six participants at the Chennai. The respondents were in the age group of 25 – 56 years (median age: 38 yrs). Of the 16 respondents, seven were women and nine were men. Of the women, three were employed part-time outside the home while all the men were employed.

There were three primary themes that emerged from the analysis of the interviews. These were, (1) mixed perceptions regarding the usefulness of the intervention, (2) preference for calls over messages, and (3) perception of the risk of unintentional disclosure.

Mixed perceptions regarding the intervention:

Participants had mixed perceptions regarding the intervention. Some considered the intervention to be helpful as a reminder to take their medications while others did not.

“We will be busy with our work, when we get busy, I feel that the reminder is very important for me to take the tablets like this, for my health.”

For others self motivation precluded the need for reminders. As the reminders were not daily they had developed their own systems to ensure that they took their medications daily. Participants knew the necessity to ensure medication adherence and the effect of non-adherence on their health.

“Once you take two medicines per day, automatically (every) morning and (at night we will remember the action)…, we start getting used to it…”
The intervention made the participants feel that they were cared for. Participants also reported the concern and support they felt from the healthcare provider as a result of the phone calls. Some perceived the calls as being from a friend and not from a machine despite all participants being aware that the calls were automated.

“When I get these computerized phone calls asking me how my health is, I feel contented… Even if I am ready to pay a hundred thousand rupees, I don’t think I will get a privilege like this…”

Preference for the IVR calls over the SMS:

Further participants preferred calls to SMSs. The interactive nature of the call, the longer alert tones and benefit of listening to a voice were reasons reported for this preference.

“The call is sufficient, SMS is not necessary, I don’t want the SMS… in the phone call they speak… to respect what they speak we (answer) the call … We do not have to respond to the SMSs… the SMS is not necessary”

Participants found it technically difficult to access the SMSs but felt that the calls were easier to respond to. They expressed a desire to speak to the person making the call.

Perception of the risk of unintentional disclosure from the intervention:

An obvious fear of stigma due to unintended disclosure of their HIV status if others received their calls or SMSs was observed. Participants ensured that they did not leave their phone unattended on the days that they received the call or SMS. Calls and SMSs were reported as advertisements when others inquired regarding them.

“…people around me wanted to know from where the call comes from. I tell them this call is from Aircel/mobile company and will try to escape from that situation.”

Some participants feared that the SMS was the “symbol” for HIV and therefore disliked the picture sent. Stigma was also one of the reasons for preferring weekly/biweekly reminders to daily or more frequent reminders.
Most participants perceived themselves as “adequately adherent” to medication. They felt that the intervention ought to be focused specifically on those who had difficulties with adherence. Stigma was an important barrier to receiving the calls in public. Preoccupied with work, the phone being switched off or unfamiliarity with the technology were also barriers identified to receiving the IVR call.

5.4 STUDY IV: COSTING OF THE mHEALTH INTERVENTION

Overall costs for the intervention were calculated by combining costs at national program level, at ART centre level and at the level of the patient. Further a sensitivity analysis based on (i) patient numbers and (ii) numbers of ART centres and (iii) components of the intervention, estimated a range of costs that may be incurred, for scale up of the intervention. The costs were calculated from unit costs incurred at the Bangalore and Mysore study centres that also implement the NACP.

Estimated intervention costs:

A cost of 371,690 INR/year was incurred at national program level for overall co-ordination and monitoring of the intervention. Similarly, a total cost of 54,450. INR/year was incurred at ART centre level (per ART centre).

A cost of 126.40 INR (per patient) was incurred at patient level for the mHealth intervention comprising of the weekly IVR call and the SMS reminder. The variable cost/patient for IVR calls only was 116.40 INR and the variable cost per patient for the SMS was 48.40 INR/patient. At scale if total patient numbers exceed 10,000 the variable costs for the intervention at the level of the patient decrease to 60.36 INR/patient/year, the variable costs for only the IVR decrease to 50.48 INR/patient/year and variable costs for the SMS decrease to 47.88 INR/patient/year.

Sensitivity analysis: The intervention cost per patient per year ranges from 91.45-110.10 INR for the IVR call and SMS combined; 81.57-100.33 INR (≈1.3USD) for the IVR call alone and 78.97-97.63 for the SMS alone based on the number of patients and ART centres deploying the intervention. This approximates to 1.2-1.7 USD (@61.95USD as of 25th December 2013).
6 DISCUSSION

The discussion is presented as:

7.1 Discussion of main findings
7.2 Methodological issues

6.1 DISCUSSION OF THE MAIN FINDINGS

6.1.1 Effectiveness of the Intervention:

A complete case analysis of study I showed that our intervention was effective in improving adherence in a cohort of HIV infected individuals already on treatment. The effect was sustained six months after the intervention was discontinued. However a best and worst-case scenario approach to the analysis provided a differing effect of the intervention over time in the study. It is possible that the true effect of the intervention was somewhere in-between.

The intervention in the RCT had no effect on both primary and secondary outcomes. There were also no subgroups identified that could benefit from the intervention; this analysis was however limited by its statistical power.

While it is possible that the intervention was genuinely ineffective, there are several probable reasons why we were unable to detect an effect in the HIVIND RCT. First, the results may be influenced by a Hawthorne effect in the study. By virtue of being a trial, the patients received additional attention as per the trial protocol. They also received additional laboratory investigations and incentives for participation and frequent follow-ups. This probably influenced adherence behavior positively regardless of the study arm.

Second, the healthy user and adherent patient bias [143] may be responsible for the absence of effect on the outcome. Literature suggests that that patients who are more likely to engage in positive health behaviors are more likely to participate in clinical trials [143]. The participants in our study were probably highly motivated to maintain a high level of adherence and hence volunteered to participate. Hence, knowing that they were in the
control arm may have prompted them to use other reminder strategies such as alarms. Another aspect that supports this argument is that the study enrolled only those who were willing to attend all study visits for two years.

Third, our intervention was automated with minimal engagement of the patient in the communication. Interventions that are more interactive, provide motivation, personal contact and social support are effective in supporting medication adherence [86, 88, 144]. Studies with interventions involving social media show effects that are enhanced by personal encounters [145, 146]. mHealth interventions for diabetes care involving two way communications and management blood glucose by healthcare providers have also met with success [60, 147]. The same may be evidenced in the WelTel trial, wherein healthcare workers contacted participants who responded with negative responses.

These effects on the outcome discussed in relation to the HIVND RCT are also applicable to the cohort study (Study I).

A significant effect of mobile phone reminders on self reported adherence was reported in two Kenyan trials [88],[89]. On the contrary, the Cameroon mobile phone trial (CAMPS) showed no effect of such an interventions on adherence [50]. A meta-analysis of these studies also indicated that mHealth interventions are effective in improving self reported adherence when optimal adherence was defined as an adherence rate of >90%. Studies that used telephone based adherence support (as against mobile phone adherence support) either reported no improvement in viral load and adherence self reports or a mixed effect i.e. improvement in only self reported adherence in the intervention group [86, 148].

In the WelTel trial [99] the two-way communication between the participant and the healthcare provider, subsequent to the SMS reminder, provided for active interaction. This may have resulted in results that differed from our study. Of importance to interpreting results from the WelTel trial is the primary outcome i.e. self-reported adherence, which is influenced by social desirability bias. Further, given that ART is necessary life long, a one-year trial may be too brief to provide sufficient evidence regarding an intervention required throughout treatment.

Another Kenyan trial studied the effect of long vs. short text message reminders and daily vs. weekly reminders against a control group that did not receive the intervention [89]. The
primary outcome in this study was adherence to ART, measured with MEMS. The study did not use viral load, a better indicator of effectiveness, as an outcome. Further, it is likely that the effect seen at an optimal adherence level of >90% may wane if the same were raised to >95%. The study also did not account for multiple comparisons of outcomes in the analysis.

On the contrary, the CAMPS trial [50] did not demonstrate an effect of the intervention on adherence. This trial sent its participants motivational messages and had an optional two-way communication component that few participants used. The participants were already on ART. The duration of this study was only six months, much shorter than the duration of the Kenyan trials and our study.

All the above trials used self-reported adherence (except one which used MEMS). As discussed before, this measure is a subjective outcome. The HIVIND RCT was the only trial that used an objective marker like time to viral failure (6months after initiating treatment) as the primary outcome. Adherence (which can only be measured with relative subjectivity) is a strongly determines viral failure (and time to failure). We chose time to failure as an outcome, as this captures most objectively any effect of the intervention that is mediated through adherence. Time to viral failure and not just viral failure was chosen, as viral failure is inevitable in all patients with time, regardless of adherence.

We also had outcomes that differed between Study I (positive effect in complete case analysis and best case approach) and Study II in this thesis. This may have been because participants in Study I were not ART naïve and most were men residing in an urban area. There was also no there was no control group for comparison of the effect seen in Study I.

Over two years non-adherence in the cohort was more likely in Mysore (univariate IRR; 0.88; CI; 0.79 - 0.97) and Chennai (univariate IRR; 0.89; CI; 0.81-0.98) in comparison to Bangalore. Despite the lower adherence in Mysore and Chennai the intervention did not affect adherence significantly at either site. This analysis however is limited by its power. Adherence rates to ART in the Indian context vary based on the demographic and health-system predictors and are reflected to some extent in our study [28, 107, 149].
6.1.2 Perceptions regarding the intervention

Usefulness:
Mixed perceptions regarding the usefulness of the intervention were observed. Some participants found the intervention useful while others did not. Participants in the WelTel BC1 study reported similar perceptions [91, 150]. As in our study, these participants also felt that they would adhere to medications irrespective of the reminder. Many participants in our study, as in other studies, used additional external cues such as meal times, prayer times and alarms even on their mobile phones [91, 150]. Some participants even used the mobile phone provided through the HIVIND RCT to receive adherence reminder calls from their spouse and family. The reminder in the HIVIND RCT was biweekly and the SMS component was not popular, in effect possibly making this a weekly reminder, it is likely that some the participants did not find such a reminder useful.

Social Support
Though primarily designed as a reminder the usefulness of the system went beyond this basic role and was perceived to provide social support. Although the intervention was automated, it was perceived to provide social support. Participants in the WelTel referred to the intervention and said that they “felt someone cares” while those in the Peruvian study called it an “angel”. Participants in our study considered it a “friend”. Computer systems are known to affect beneficiaries in ways not conceived by their inventor [151]. Human–computer interaction studies have shown that beneficiaries tend to give computer systems an anthropomorphic character [152]. Similar psychological reactions are reported to occur, irrespective of whether the personality interacted with is human or embodied in technology [152]. Research indicates that beneficiaries can decipher social, emotional and intellectual cues embedded in a computing interface [151]. Our intervention by referring to itself as a friend provided the patient with a social cue interpreted as social support. Also, marginalization resulting from HIV infection probably makes any additional support, however trivial, a welcome alternative. mHealth interventions are generally welcomed for the various forms of support they are perceived to provide.

Marginalization:
Participants feared the disclosure of their HIV sero-status as a result of the intervention. Marginalization resulting from stigma is a known cause of such fear. Similar findings have been reported in other studies that have explored mHealth for HIV infection [95].
Participants therefore request for messages that conceal the true intent of such communication [153]. Researchers have also tried to alleviate such fear by designing interventions that do not use words such as ‘HIV’, ‘disease’, ‘hospital’ etc. One study from Peru [95] sent patients an ART adherence reminder that said ‘it’s the time of your life’, the Kenyan WelTel study [154] called the patient with the message ‘mambo’ which means ‘how are you?’ In the HIVIND RCT, the IVR did not refer to any disease while the picture SMS depicted a lamp. Despite this, participants kept the phone on their person on the days of the reminder, did not respond to calls in public and reported that the call was for alternate purposes in an effort not to divulge the source of the call. Studies have reported participants withdrawing consent [155], not responding to calls when in public [156] and deleting SMS texts from the fear of disclosure of their HIV sero-status [63]. Interventions that use “context aware” mobile technologies, i.e. technologies that can identify the users location, time of the day, neighbouring users and the users activity to personalize communication [157]. The use of such technology in low-middle income country (LMIC) contexts even if efficacious, could pose financial constraints. Instead, researchers and technology developers need to collaborate to design contextually appropriate interventions.

Preferences:
The IVR call alone or the combination of the IVR call and the SMS was preferred to only the SMS reminder in our study, both in the pilot and in the trial. In the pilot a greater number of participants reported that the IVR call was helpful in comparison to the SMS. The engagement, though limited, provided by the IVR call when compared to the passivity of the SMS was one of the reasons for this preference. The limited literacy in the Roman script limits the use of SMSs in our setting [75, 158]. With this in mind a pictorial reminder SMS was developed. Yet, despite being pictorial, non-accessed SMSs were found in participants’ phone-inbox at in-depth interviews. Participants’ considered the SMS cumbersome to access, probably due to limited exposure to the technology. Though, SMS is popular among younger people in India, those who are older prefer voice calls [75]. This may be because the skills necessary for SMS communication, such as, literacy, language, the ability to understand the content and phone menus, decision-making and cognition are limited in those with limited exposure to mobile phones [159]. Most mHealth interventions globally use SMS technology [49]. Both IVR and SMS technology used in a RCT was perceived as being difficult to operate in an RCT that compared the two types of communication for adherence monitoring [160]. Contextual differences regarding preferences for the mode of communication exist [76, 150, 161]. This reflects the need to
identify the desired mode of communication to be incorporated into mHealth interventions in specific settings.

_Privacy:_
Privacy concerns regarding mHealth interventions have been raised [162-165]. However few of these are applicable to our intervention. Concerns could arise when phones were left unattended or lost and hence accessed by third parties with the potential for causing unintended disclosure of HIV sero-status. Though, persons other than the patient accessed the intervention none reported such unintended disclosure. Further, lost phones were immediately reported and the participants provided the study site with alternate phone numbers to receive the intervention. When in a situation that had the potential for disclosure of their HIV sero-status, patients reported that the calls were either from the network provider or their healthcare provider for diseases other than HIV infection. Further, as the intervention was automated as a result reverse dialing the number from which the call was received did not provide a response, thus avoiding disclosure of any information to inquisitive third parties.

The possible breach of privacy as a result of obtaining personal-identifiers is not relevant to our intervention as we did not collect such information via the phone. However, for the purpose of delivering the intervention the participants study enrollment numbers and phone numbers were entered on a database operated by the network provider. This was a closed circuit inaccessible network accessible only with study site-specific passwords. Participants preferred this system in comparison to involving a third party who had to be made aware of the patients HIV sero-status in order to make the calls.

_Intrusiveness:_
Studies report mobile phone reminders to be intrusive if too frequent [166]. The participants did not consider the intervention intrusive. Intrusions from persistent calls due to technical issues were ignored as the calls were from the healthcare provider. Further, most participants were willing to accept the intervention in the frequency it was provided. This reflects not only on the patriarchal nature of the patient-provider relationship in the Indian context [167-169] but the acceptability of additional support in any form from the healthcare provider.
6.1.3 Costs of the intervention:

The costs for scale-up per patient were low both for the individual components and the combined intervention. There were a few factors associated with low costs in our study (i) the costs for mobile phone communication in India is one of the lowest in the world (ii) these costs decrease as the number of patients increase (iii) the software used by the technical solution providers did not require large investments on user licenses (iv) a competitive bidding process identified a technical solutions provider with the lowest cost for developing and deploying the intervention (v) intervention design was simple and did not require complex IVR algorithms.

Costs of mobile phone interventions however will vary based on the context. One study from Swaziland reports that despite the low cost of text messaging at 0.80 SZL (0.06 GBP) funding with the health system is limited and may be not support the costs of mHealth interventions for HIV infection [170]. The Kenyan WelTel study reports a cost of 2.6 million USD for 0.4 million patients receiving ART in 2009 at 8 USD/patient/year [171] . These costs are higher than those incurred in our study but may be attributed to the intervention design that involved active follow-ups via mobile phones. Also detailed cost calculations for the WelTel study are not available for comparison. Studies indicate that monthly costs of alternate interventions such as pagers, beepers and alarms inclusive of equipment batteries, service, utility and clinic based costs ranged from 34-133USD [172]. These costs are however calculated from the patient’s perspective.

Another strategy is directly observed treatment (DOT). It is probably the only strategy that can confirm with certainty that the patient has ingested the medication. While the efficacy of DOT is questionable in tuberculosis [173], studies for DOT in HIV treatment have shown promising results [174]. However the costs of DOT can be prohibitive. Costs for clinic based directly observed treatment for HIV infection for 5-days could range from 557 USD to 780 USD/month. The costs varied with the setting (home based) and frequency of observation (twice daily) [172]. These costs should be viewed in the light of the healthcare context, the disease they target and the time period in which they were assessed. In comparison the costs of mHealth technologies would be much lower given the ubiquity of mobile phones. This provides healthcare programmes with the opportunity to only deliver the intervention without investing in dispensing mobile phones, considerably saving costs. Further interventions that give patients missed calls [170] intended as reminders could be
explored. Such interventions could save costs markedly if their effectiveness beyond that of an alarm is proved.

While we did not assess the cost effectiveness of our intervention as the intervention was not effective, the study provides a model to assess costs incurred with mHealth interventions. However, the model may be varied based on the healthcare context and the type of intervention. Given the new impetus of the Indian government to use mobile communications technology in healthcare, the costs may be adapted to the need.
6.2 METHODOLOGICAL ISSUES

6.2.1 Study 1

Adherence Measures:
The primary outcome was adherence measured by the pill count. The pill count is an objective measure of adherence where in the adherence rate is calculated based on the number of pills returned. It requires that the patient carries the pill container every time a refill is necessary. In our study, as is it mandatory to return the pill container at a pill-refill as per the existing standard of care requirements, patients ensure that they do not forget taking the container.

However, pill counts may be inflated due to social desirability bias [146]. Patients are known to discard pills, “pill dumping” to appear adherent. Lost pills, extra pills taken and sharing pills could also inflate adherence. We questioned patients regarding lost pills and additional pills taken to minimize this. Separating pill count assessments from adherence counseling allays the fear of being reprimanded during counseling, minimizing the need to appear adherent. We followed this procedure with the pill count assessments in our study. While pill counts could be substituted with technology such as MEMS [175, 176], its costs posed constraints. Further, mere opening the pill bottle does not imply that the pills were taken. Therapeutic drug monitoring (TDM) provides a more accurate assessment of adherence in comparison to pill counts in most disease. However inter-individual variability in the blood levels of ART and the cost of such assessments prohibit its use [125]. NRTIs are metabolized within cells and therefore do not qualify for TDM. The bioavailability of NNRTIs could be affected at absorption in the gut, also synergistic, antagonistic additive effects of drugs used in combination prevent accurate assessments. While these limitations are primarily pharmacological, patients might further bias the estimates by taking their pills just prior to assessment [146].

Other popular methods of adherence assessments in research are patient self-reports such as four day recall, visual analogue scale and Morisky scale. These are subjective assessments,
more prone to social desirability bias than the pill count. In addition, they are also subject to recall bias especially when the pill burden is high.

**Analysis of missing values:**

An attrition rate of 6% was observed in this study along with some data missing at different time points for the outcome variable. To address this attrition bias, missing data was considered missing at random and [177] replaced with best and worst case scenarios in a sensitivity analysis. As such assumptions are too strong, the sensitivity analysis provided a range of estimates within which the true outcome probably lay [177]. Much debate exists surrounding data imputation. The misconception that imputing data is akin to “making up data is common in research [178]. Imputing data involves replacing missing data based on assumptions to maintain the important characteristics of the data set without the loss of statistical power [178]. With the availability of statistical software and newer methods of imputing data, missing data may be replaced both within and across waves (data collection time points) of data collection [179, 180]. Though we did not use advanced statistical methods for imputation, we did replace missing data across all waves in the analysis.

### 6.2.2 Study II:

Based on the PRECIS tool, the HIVIND trial lies closer to the pragmatic end of the pragmatic - explanatory continuum [181]. Factors that favoring ‘pragmatic’ are that all participants received the usual standard of care available in the setting, there was a degree of flexibility in implementing and monitoring the intervention, site-specific protocols (e.g. differing medication regimens at the study centers) with regards management of patients and intention to treat (ITT) was used in the analysis. The factors favoring ‘explanatory’ are strict enrollment criteria, rigorous follow-ups and protocols and a trial outcome requiring specialized assessment techniques not routinely used in HIV care.

The study was implemented at three centres that differed with respect to the motivation to provide care. One was a public tertiary level teaching healthcare facility, the second a private not for profit tertiary level teaching facility and the third a private HIV care and research facility. These facilities attract a varied clientele, as the services are free of cost in public healthcare or at a cost to the patient in the private healthcare. This represents the
existing spectrum in Indian health system for treatment of HIV infection and promoting the generalizability of the results of the HIVIND RCT.

The trial protocol required, rigorous monitoring of participants adherence and clinical outcomes. It provided participants with additional laboratory investigations and dietary assessments that are not available to routine patients. There were also stringent retention protocols. Additionally all participants received a mobile phone and airtime. This probably encouraged participants, even in the control group to adopt positive adherence behaviors [182], implying the possibility of a Hawthorne effect in the trial and mitigating the improvement in trial outcomes in the intervention arm.

The adherence levels measured by pill count were high throughout the study. The adherence measurements in this study are subject to the same bias as in Study I.

Given the inherent biases with pill count discussed under Study I, we chose viral failure as a surrogate end point in the trial. Viral load is an objective biologic marker in the direct causal pathway of the disease process, adherence is highly predictive of time to viral failure and influences the viral load. The time to viral failure therefore fulfills the requirements of a surrogate end point [108, 183, 184].

The intervention did not function 100% of the time. There were two major episodes when the IVR call was discontinued for upto 2-3weeks. This occurred when the intervention providers switched between network providers. This also affected SMS delivery. However reports indicated that nearly 40% of the SMSs were not delivered despite being sent. This may have been due to poor networks, the phone being switched off or being out of network coverage area. Given that many participants did not view the SMS, this may not have affected the patients medication taking routine.

We performed an intention to treat analysis [185] (ITT) on the study outcomes as we wanted an accurate estimate of the outcome in the ‘real world setting’. This means that all those who were randomized were included in the analysis in the arm to which they were randomised. ITT also provides an unbiased and conservative assessment of outcomes based on the observed levels of protocol adherence within the trial [185]. The HIVIND trial tried to assess the effectiveness of the intervention in the real world setting, unlike efficacy trials, that study outcomes in under ideal conditions. The ITT analysis suits this purpose [185].
6.2.3 Study III:

This was a qualitative paper analyzed using Framework analysis [186]. As the interviews were conducted prior to data analysis in study II (HIVIND RCT) the adherence status of the participants in this study was unknown at the time of the interview. The study does not explain why the intervention did not have an effect on adherence but focuses on the perceptions regarding the intervention.

The framework approach to analyze qualitative data used in this study is ideal for such data from health systems [186]. It is poised between inductive and deductive approaches and helps understand the perceptions of participants in the light of the researchers experiences [187].

**Reflexivity:**

Reflexivity is the self-awareness of the researcher regarding the relationship between themselves and their research environment [188]. It requires that the researchers understand their own position and the perceptions arising thereof in the process of research.

As a physician involved in community medicine, I had the experience of taking healthcare to the people in the community both in urban and rural India. Also, as a researcher in the community I have had experience with data collection at household level. In doing so, I had an insight into the lives of patients, their environment and the factors influencing their health. This influenced me to relate to them in a way put them at ease during the interview. It also helped me understand their perceptions regarding the intervention and helped me choose appropriate questions during the interview.

As a physician involved with implementing the HIVIND study (Study I and II), I had the opportunity to follow up and interact with study participants. The participants shared their experiences of being a PLWHIV with me. This increased my sensitivity to those with the illness.

As a researcher involved with ensuring the fidelity of the intervention I received the IVR calls and SMSs that the patients received. Hence I too had the opportunity to receive and respond to the call, respond to people enquiring regarding the call. I had the experience of receiving multiple calls and being unable to respond to the calls due to various reasons.
Simultaneously, I also understood the provision of this service from a healthcare providers perspective.

As a person with a mobile phone I understood the concepts of intrusiveness, privacy and confidentiality that all of us experience every day with mobile phone communications.

Further as a researcher experienced in public health I approached the data with this perspective. In addition it was useful to obtain behavioral science and clinical perspectives from the co-authors.

**Trustworthiness:**
For this study to be recognized as making a distinctive contribution to mHealth, it is necessary to enunciate the steps taken to ensure its trustworthiness. These are described under credibility, transferability and dependability as per the framework put forward by Guba et al [189].

**Credibility:**
Considered as one of the most important factors contributing to trustworthiness it indicates whether the researchers actually studied what they intended to. To ensure credibility the interview guide was developed by the first author and modified based on suggestions from the last author. The interview guide was subsequently pretested and modified prior to conducting the interviews. The interviews were audio-recorded to ensure that the conversations were captured accurately. These were transcribed and translated by a native speaker familiar with the English language, the transcripts were spot checked with the audio recordings to ensure accuracy. Further, the last author reviewed the framework developed by the first author. The last author also checked that the codes identified by the first author matched those in the framework. The first and last author developed the subthemes and themes over several iterations. These were then shared with all authors and modified based on their feedback.

**Transferability:**
Transferability is the ability to apply research findings to another context. To promote transferability the study participants were chosen to represent the different demographic profiles prevalent in the region and the HIVIND RCT. In the manuscript the authors describe the regions and the study centers involved. The study is also described in the
context of main HIVIND RCT, the participant perceptions within which it sought to describe. A thick description of the context is given for the readers to judge whether any of its findings may be applicable in their setting.

*Dependability:*
To ensure dependability, all processes and procedures employed for data gathering and analysis are explained in detail under the methods section in the manuscript for Study III

### 6.2.4 Study IV:

This paper involved assessing costs for the mHealth intervention in the HIVIND trial from the perspective of scale up by the NACP. The costs were calculated for a five-year period; i.e. one cycle of the NACP. No discounting was used as costs were calculated for a short period. Sunk costs i.e. costs that involve buildings, land etc. were not used. We did not consider costs incurred for trial implementation as they would not be incurred in a national program setting. Further, as we intended to inform policy we used the healthcare providers’ perspective and not the societal perspective. All costs were reported in Indian Rupees as these refer specifically to the Indian context. The costs in other contexts will vary based on the costs of mobile communication, the type of healthcare system and the complexity of the intervention or the problem they target. The costs were calculated for the number of patients expected to be on treatment based on the existing Indian guidelines for initiating ART. The study did not account for an increase in the number of patients if the CD4 threshold at which ART is initiated is raised from 350 cells/cumm to 500 cells/cumm as per international guidelines [3].
7 CONCLUSION

The mHealth intervention showed promise when investigated for feasibility. However, we were unable to detect an effect on time to failure and adherence to treatment in the RCT. The effect on adherence was irrespective of the varying adherence levels seen at different centers within the study. Despite its ineffectiveness in the trial, participants considered the intervention helpful. Mixed perceptions regarding the intervention and a need for engaging in two-way communication were observed. The fear of marginalization from unintended disclosure of HIV status through the intervention is a cause of concern. The risks of such disclosure need to be weighed against the benefits of such interventions prior to their deployment, even if efficacious. The costs of such an intervention targeting other aspects of HIV care is low.

Implications for Research and policy:

This thesis aimed to provide evidence regarding the role of mobile phones for adherence support to antiretroviral therapy in an Indian setting. Though the results of the study did not detect an effect of the mHealth intervention on the outcome, it does not imply that mHealth interventions do not work. mHealth interventions designed to target specific populations such as those with poor adherence may be successful. It is considered necessary that the design process for these interventions involves exploring the need and acceptability of prospective interventions. Further, feedback obtained with preliminary studies could inform the design of the interventions under development. Design considerations should also involve factors such as personalization, frequency, interactivity, ease of use of the intervention and designs that support privacy and confidentiality, especially in sensitive disease such as HIV infection. Further, for success of an mHealth intervention, designs should be developed in the context of existing behavioral theories. A multidisciplinary team comprising physicians, IT professionals, behavioral scientists, social scientists and the patients themselves can enable this.
A need for development of policy to safeguard the privacy and confidentiality of patients involved in mHealth interventions is necessary, given, the global popularity of the mHealth interventions and the existing issues with using public networks for communication.
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