Cost effectiveness of simplified HCV screening-and-treatment interventions for people who inject drugs in Dar-es-Salaam, Tanzania

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Tables: 3

Figures: 2, Supplementary Figures: 3

References: 49

Keywords: HCV, cost effectiveness, sub-Saharan Africa (SSA), people who inject drugs (PWID)

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Abstract

Background

Compared to other countries in sub-Saharan Africa, Tanzania has a relatively progressive illicit drug harm reduction (HR) policy, through a predominantly opioid substitution therapy-based programme. However, access to hepatitis C virus (HCV) diagnosis and curative direct acting antiviral therapy remains elusive. We developed a cost-effectiveness model to evaluate a simplified HCV screening-and-treatment intervention among PWID in Dar-es-Salaam, Tanzania.

Methods

A decision tree and Markov state transition model compared existing practice (no access to HCV viral confirmation and treatment) with the integration of point-of-care HCV screening and treatment within (1) existing HR services and (2) expansion to include PWID not currently engaged in HR. Outcome measures were screening, treatment, HR and disease-related costs per PWID, quality-adjusted life years (QALY) and disability adjusted life years (DALY). Cost-effectiveness was evaluated from a healthcare payer's perspective over a 30-year time horizon over a range of willingness-to-pay thresholds (USD$273 to USD$1,050). Both deterministic and probabilistic sensitivity analyses have been conducted.

Results

Assuming a chronic HCV prevalence of 18.8%, screening-and-treatment in existing HR settings resulted in an ICER per QALY-gained and DALY averted of USD$633 and USD$1,161, respectively. Expanding to include an outreach programme for unengaged PWID yielded an ICER per QALY-gained and DALY-averted of

USD$4,097 and USD$10,288. Factors affecting the sensitivity of the ICER value included the cost of HR and the health utility of non-cirrhotic disease states.

Conclusion

Simplified HCV screening and treatment of PWID has the potential to be cost-effective in Dar-es-Salaam, Tanzania. In practice, synergism of human and financial resources with established health programmes may offer a pragmatic solution to minimise operational costs.

Introduction

It is estimated that chronic infection with hepatitis C virus (HCV) among people who inject drugs (PWID) is responsible for almost half of all incident HCV-related infections and a third of deaths globally (Degenhardt et al., 2016; Trickey et al., 2019). Consequently, addressing the HCV epidemic among PWID is considered imperative in order to come close to achieving the HCV elimination target by 2030 (Heffernan, Cooke, Nayagam, Thursz, & Hallett, 2019), which includes increasing access to harm reduction (HR) (300 clean syringes per PWID annually), 90% diagnosis and 80% treatment (World health Organisation, 2016). Injecting drug use is an under-studied issue in sub-Saharan Africa (SSA), where it is estimated that close to 10% to the global PWID population reside (Degenhardt et al., 2016).

Although there is an increasing trend in injecting drug use globally, a recent systematic review reported that the largest increase has been reported in SSA (Degenhardt et al., 2017). Though increased awareness and reporting of injecting drug activity may account for some of this rise, the overall incremental trend is likely to be genuine. Socioeconomic factors coupled with political disinterest and suboptimal access to healthcare synergise to propagate the problem (Uchtenhagen, 2004). Despite these concerning facts, access to HR across SSA remains poor (Harm Reduction International, 2018). In such settings, high-risk practices (such as equipment sharing) are commonplace among sub-groups of PWID not engaged in HR, where chronic HCV prevalence has been reported as high as 90% (Harm Reduction International, 2018).

There are approximately 12,000 PWID living in Dar-es-Salaam, Tanzania (Tanzania National AIDS Control Programme, 2014). Over the past decade the government has

collaborated with international donor projects such as the United States President's Emergency Plan for AIDS Relief (PEPFAR), to provision access to HR for PWID. To date, opioid substitution therapy (OST) remains the mainstay of addiction management, with an estimated 5,000 PWID having registered for support across three main clinics in Dar-es-Salaam. Individuals attending the clinic are required to remain abstinent from all illicit drug use. They have access to clinical and psychiatric care, formal screening and treatment for HIV, TB and vaccination against HBV. In addition, the non-governmental organisation Médecins du Monde run an independent needle and syringe programme (NSP) in Dar-es-Salaam, which supports approximately 500 PWID. It is important to note that as both OST and NSP are being operated by independent organisations and minimal combined HR exists in Tanzania.

A recent cascade of care for PWID engaged in OST in Dar-es-Salaam estimated that the anti-HCV prevalence was 31%, with over half of these individuals still regularly attending the clinic and three-quarters of whom underwent a clinical assessment (considered to be linkage-to-care) (Mohamed et al., 2018). Despite being the most prevalent blood-borne viral infection, the provision of HCV care is limited to anti-HCV screening, with no access to essential nucleic acid testing (NAT) to confirm viraemia. In addition, there is no access to interferon therapy or direct-acting antivirals (DAAs), resulting in multi-level failure of retention along the cascade of care (Mohamed et al., 2018). In-field validation of the Xpert® HCV fingerstick viral load (Xpert® HCV FS VL) and HCV core antigen quantification (HCVcAg) using plasma, dried blood spots (DBS) and capillary whole blood have now provided practical and financially tangible alternatives to conventional NAT for resource limited settings (Mohamed et al., 2020; Mohamed et al., 2017). Meanwhile, increasing access to low-cost generic DAAs make

treatment a realistic prospect in the near future in SSA. Indeed, empirical evidence confirming excellent DAA efficacy is beginning to emerge from population interventions in SSA including; Rwanda, Sénégal, Cameroon and Côte d'Ivoire (Gupta et al., 2019; Lacombe, 2018). However, the uncertain cost of implementing HCV screening and treatment is still felt to be a significant barrier to many countries' ministries of health including such an intervention as part of their agenda.

With potentially amenable solutions to these challenges on the horizon, it is imperative, in such resource-limited settings, to gain an appreciation of the financial implications and benefits of averting health-related complications of any proposed screening and treatment intervention. We have recently reported the population-level modelling outcomes of scaling-up HR and treatment of PWID in Dar-es-Salaam, Tanzania (Scott, 2019). This study estimated that various treatment programmes could reduce annual incidence among PWID by 57-73% by 2030 and reduce the projected 2030 prevalence among PWID from 27% to 5-9%, with enhanced impact if combined with HR expansion. However, this model did not focus on the different approaches, especially their cost-effectiveness, to implement such a programme in both HR and community settings. Incorporating previously published data for both HCV disease profile (Mohamed et al., 2018) and validation assessment of two diagnostic tests for HCV viraemia (Xpert® HCV FS VL and HCVcAg) among PWID in Dar-es-Salaam, Tanzania (Mohamed et al., 2020; Mohamed et al., 2017) , we aim to evaluate a decision tree and Markov model to determine whether; *(a)* using novel and simplified diagnostics and scaled-up HCV treatment among PWID engaged in HR and *(b)* expanding screening and treatment among PWID not engaged in HR, are cost-effective strategies in Dar-es-Salaam, Tanzania.

Methods

Model Structure

The cost-effectiveness of an HCV screen-and-treatment intervention was assessed among the PWID in Dar-es-Salaam, Tanzania. A closed-cohort Markov model was designed to generate cost (USD$) and health-utility outputs (quality adjusted life years (QALY), disability adjusted life years (DALY)) over a 30-year time horizon using TreeagePro® (Williamstown, MA) modelling software.

All PWID entered the model at the first cycle and encountered three decision nodes; (1) engagement in HR, (2) screening assessment and (3) treatment (for viraemic individuals). Baseline data for prevalence of chronic HCV infection and distribution of chronic liver disease has been derived from existing literature for PWID engaged in HR in Dar-es-Salaam (Mohamed et al., 2020; Mohamed et al., 2018). Data from existing meta-analyses provided the rate of HCV-related liver disease progression and mortality (Smith, Combellick, Jordan, & Hagan, 2015; Thein, Yi, Dore, & Krahn, 2008) used in the Markov state transition model. A further detailed description of the clinical setting, model structure and referenced tabled of input variables can be found in Table 1.

Model parameters

On entry to the model all PWID were stratified by whether they are engaged in HR (90% OST and 10% NSP) or not. On the basis of recent validation of the Xpert® HCV RNA VL assay in this population, the chronic HCV RNA prevalence was set as 18.8% (Mohamed et al., 2020). On entry into the model the vast majority of chronically

infected individuals (83%) had mild liver (F0/F1) disease while 5% had compensated cirrhosis, as described in existing literature of PWID engaged in HR (Mohamed et al., 2018). As there is a lack of data for those not engaged in HR, it has been assumed that these parameters were equivalent to those engaged in HR.

In the absence of local epidemiology reporting the rate of disease progression in this cohort, it has been assumed that this is in-line with the mean rate reported in existing meta-analyses in well-resourced settings (Smith et al., 2015; Thein et al., 2008). Among individuals undergoing treatment, progression of disease was halted in pre-cirrhotic states, while cirrhotic individuals continued to experience ongoing disease related complications (decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). DAA failure and persistent viraemia resulted in continued progression of disease at the same rate as untreated individuals. Given the high-risk status of the population it was assumed that the transmission of disease has occurred as a result of injecting drug use. In addition to disease specific morbidity and mortality, a standardised mortality rate has been applied to all individuals entering the model (Larney et al., 2017). A supplementary analysis (Supplementary Table 1) has been conducted to assess the effect of a fixed rate of reinfection after curative therapy. A summary of the HCV liver disease model is presented in Supplementary Figure 1.

Interventions

Table 2. summarises the approaches for the three strategies tested as part of the model. The strategy A reflects the existing standard of care, where only those engaged in HR undergo baseline anti-HCV screening, however this does not result in any linkage-to-care and treatment uptake and results in progression of liver disease,

disease-specific and background mortality over the model lifespan (30 years). We then considered two screening and treatment scenarios, for each case screening and treatment are completed in the first year (first cycle) of the model. Strategy B incorporated data from this cohort, validating POC Xpert® HCV FS VL in anti-HCV positive individuals engaged in HR (Mohamed et al., 2020) and treating 80% of those with viraemia with DAA therapy, and assumed a sustained virological response (SVR) 12 weeks post treatment of 95% in line with existing data on treating PWID (Dore et al., 2016; Grebely et al., 2018). Those with chronic HCV who defaulted from HR or currently are not engaged in HR were not treated and a proportion experience morbidity and mortality as described in strategy A. Finally, in addition to scaling-up treatment in PWID accessing HR (strategy B), Strategy C incorporated decentralised screening using HCVcAg DBS in 50% of PWID not engaged in HR as part of a hypothetical outreach screening programme. A Bayes' revision was applied to account for the sub-optimal sensitivity (76%) of HCVcAg DBS (Mohamed et al., 2017). To avoid false negative results, all HCVcAg DBS cases underwent confirmation using Xpert® HCV FS VL testing (Mohamed et al., 2017). Accounting for the potential delay in diagnosis, 50% of viraemic individuals screened using HCVcAg DBS initiated treatment, with 95% achieving Sustained Virological Response (SVR) 12 weeks after the end of treatment (SVR12). All individuals engaged in treatment were assumed to be simultaneously enrolled in HR.

Costs ($USD) and utilities

A health-care payer's perspective has been assumed for the input variables used in this model. A micro-costing approach has been undertaken to most accurately reflect anticipated added costs of a scaled-up HCV intervention. For screening this included

the HCV assay costs and a cost for additional clinical resources to conduct phlebotomy, liver disease assessment and counselling of viraemic individuals linked-to-care. In outreach screening, an additional cost has been included to reflect the additional resources required for the intervention (Meehan, Beyers, & Burger, 2017). Furthermore, an estimated cost of generic DAA therapy and also included follow up clinician assessment and HCV RNA costs at end-of-treatment and SVR12 timepoints have been included for treated individuals. Country-specific liver disease stage-specific costs have been obtained from existing literature (Chhatwal et al., 2018). Finally, the annual weighted-cost of HR (90% OST and 10% NSP) has been applied to those actively engaged in these services (Medecins Du Monde, 2018; Scott, 2019; Wilson, 2014). A breakdown of all costs can be found in Table 1.

In this model disease states are assigned disability weights (determined from the global burden of disease study) (Stanaway et al., 2016) and health-related quality of life data from existing literature (Shepherd et al., 2007; Wright et al., 2006). These values are used to generate DALY and QALY outputs of the model respectively as presented in Table 2. Both cost and health utilities have been discounted at a rate of 3% per annum (World Health Organisation, 2003) and a half-cycle correction has been applied to initial and final cycles.

Estimation of cost-effectiveness

Using Strategy A as the baseline comparator, an incremental cost effectiveness ratio (ICER) was generated for the proposed alternative strategies. Unlike in high-income settings, the threshold ICER for cost-effectiveness is less well agreed. Three cost effectiveness thresholds are considered; (conservative) 0.26-multiple (USD$ 273),

(moderate) 0.5-multiple (USD$ 525) and (liberal) 1-multiple of the per capita gross domestic product (GDP) of Tanzania (USD$1,050) (J. Ochalek, Lomas, & Claxton, 2018; J. M. L. Ochalek, J.; Claxton K.P, 2015). In addition, outcomes cumulative cost and utilities are presented as alternative comparators between strategies.

Sensitivity analysis

A sensitivity analysis has been conducted to ensure the robustness of the results generated from the model. Table 1 presents point estimates derived from an established PWID cohort attending the OST clinic at Muhimbili National Hospital, Dar-es-Salaam, Tanzania (Mohamed et al., 2020; Mohamed et al., 2017; Mohamed et al., 2018). In addition, the upper and lower bounds used for both deterministic analysis and probabilistic sensitivity analysis (PSA), with the relevant references listed. Reference bounds without a suitable reference ranges have been simulated using either expert opinion or by a 20% adjustment. Health utility values used to derive QALY outputs have been subjected to a restriction to prevent negative utility among treated individuals. Given the paucity of HCV epidemiological data for PWID in Tanzania, a uniform sampling distribution for the input parameters was used to provide to account for the broadest level of uncertainty. A Monte Carlo Simulation has been conducted to generate 1,000 randomised events for the PSA.

A supplementary sensitivity analysis has been included to assess the effect of a fixed rate of reinfection among successfully treated PWID on the cost-effectiveness of the interventions. Finally, a disaggregation of the community-based screening arm of strategy C has been conducted. In this sub-analysis, HCVcAg screening and secondary confirmatory testing is replaced by simplified Xpert® screening at

equivalent uptake (50%) and improved uptake to match HR screening in strategy B (76%).

Results

Cost-effectiveness of scaling-up screening and treatment of HCV infection

The cost-effectiveness outcomes for all strategies over a 30-year period, based on a cohort of 12,000 PWID in Dar-es-Salaam, are displayed in Table 3. When compared with the existing standard of care (strategy A), the introduction of an HCV screening and treatment programme into existing HR services in Dar-es-Salaam (strategy B) resulted in 293 (13.3%) HCV-infected individuals receiving treatment and the projected health-related benefit was reported as a total of 720 QALY gained or 360 DALY averted. A total of 575 (25.5%) of HCV infected individuals received treatment through expanding screening and treatment in the community for those not currently engaged in HR (as proposed in strategy C), resulting in 1,200 QALY gained or 480 DALY averted.

The annual cost associated with strategy A was estimated to be USD$694,528 (screening (upfront); USD$8,280, treatment; USD$0, disease related; USD$71,784 and harm reduction; USD$622,468). While the annual cost for strategy B was calculated at USD$710,616 (screening (upfront); USD$84,480, treatment (upfront); USD$80,880, disease related; USD$70,368 and harm reduction; USD$634,736). Finally, the annual cost for strategy C was USD$865,216 (screening (upfront); USD$295,320, treatment (upfront); USD$160,440, disease related; USD$68,448 and harm reduction; USD$781,576).

Overall, restricted screening and treatment within existing HR settings (strategy B) returned the most favourable ICER per QALY gained (USD$633), while the ICER per DALY averted was USD$1,161 for this strategy. An expanded screening and treatment programme to include those currently not registered in a HR programme (strategy C) results in an ICER of USD$4,090 per QALY gained and USD$10,288 per DALY averted.

HCV-related disease morbidity and mortality

At entry into the model, four-fifths of HCV-infected individuals had mild liver related disease. However, without HCV treatment after 30-years the model indicated that the liver disease profile of those with chronic HCV shifted to reflect a more advanced liver disease (26.1% cirrhotic) and associated complications (2.0% DC and 2.0% HCC). In comparison, in the cohort who underwent successful DAA treatment, the majority of patients continued to remain in the mild disease category (51.8%). In addition, overall mortality in both untreated and treated groups was similarly high (36.7% vs 35.7%). The morbidity and mortality profiles for untreated and treated individuals is in supplementary Figures 2a and b.

Sensitivity analysis

Figures 1i-iv summarises the variables, which have the largest influence on the ICER per QALY gained or DALY averted as part of the deterministic sensitivity analysis for both limited (strategy B) and expanded (strategy C) screening and treatment. The assumed inclusion of the cost of HR (baseline USD$890) as part of standard of care, results in a universal reduction in the ICER values, which fall below or in line with the most conservative WTP threshold ($USD 273) apart from the ICER per DALY averted

for strategy C. Furthermore, for strategy B improved health from treatment in mild (F0-1) and moderate (F2-3) disease states resulted in an ICER per QALY gained below the moderate WTP (USD$525) and an ICER per DALY averted below the liberal WTP (USD$ 1,050).

When reinfection at 2.8% per annum (Muller, Vlahov, Akiyama, & Kurth, 2020) was tested in a sensitivity analysis (see Supplementary Table 1) the ICER per QALY-gained and DALY-averted for strategy B was USD$761 and USD$1,196, while it was USD$5,019 and USD$11,881 for strategy C. The simplification of community screening in strategy C resulted in reduced costs of testing (per PWID cost USD$10.05-12.23), while increasing the uptake of testing from 50-to 76% resulted in an increased per PWID QALY-gained (2.99) (Supplementary Table 2).

The results of the PSA cost-effectiveness acceptability curve (Figures 2a and b) revealed that scaling-up screening and treatment in HR settings (strategy B) became the dominant strategy at an ICER per QALY gained of USD$607 and DALY averted of USD$1,273. The ICER scatterplots are presented in Supplementary Figure 3a to d). A reported 73.1% and 47.4% of QALY and DALY-based iterations fell below the liberal WTP threshold (USD$1,050). Expansion to include community-based screening and treatment (strategy C) was less cost-effective with an ICER per QALY gained of USD$5,878 and per DALY averted of USD$10,835, with 23.9% and 12.9% of QALY and DALY-based ICER iterations falling below the liberal WTP threshold.

Discussion

The integration of HCV screening and treatment into the existing HR programme for PWID in Dar-es-Salaam, Tanzania, could result in a net gain of 720 QALY, 360 DALY averted, while expanding screening and treatment to include PWID not currently engaged in HR might generate a net gain of 1200 QALY, 480 DALY averted. A series of WTP thresholds (conservative, moderate and liberal) were set with reference to the Tanzania GDP. Of the base-case ICER values, only the ICER per QALY for strategy B (limited screen-and-treat intervention within existing HR (USD$633)) fell below a liberal WTP threshold (USD$1,050). The sensitivity analysis identified cost of HR as the most important contributor to the overall ICER value, with all strategies generating results between the 'liberal' and 'moderate' WTP thresholds (USD$ 273 to 525) when these costs were considered as part of standard of care.

To date cost-effectiveness analyses of HCV screening-and-treatment in Africa have been limited to population-based interventions (Boyer, 2018; Hecht et al., 2018; Kim et al., 2015), with one making reference to HR and treatment of PWID (Scott, 2019). Our model provides a more focused evaluation of tailored HCV screening and treatment strategies within the PWID community in Dar-es-Salaam. A particular strength of this Markov model is that it includes epidemiological and virological data collected from the local PWID population in Tanzania (Mohamed et al., 2020; Mohamed et al., 2017; Mohamed et al., 2018).

The various elements that combine to determine the overall cost of implementing HCV screening and treatment are important factors in this model, especially given the resourced-constraint setting. In particular, the provision of HR (OST and NSP), which is responsible for the highest proportion of the total costs of each strategy (90%). This

has a significant impact on the expanded community-based screening and treatment strategy (strategy C). Although there is an associated increase in treatment uptake, this is eclipsed by a steep rise in costs of HR as all screened individuals are assumed to be simultaneously enrolled in HR. Furthermore, the added direct benefits of HR are not taken into account at all as part of this model. As a consequence, the ICER values generated for this intervention were unfavourable. It is likely that this is an over-estimation, as many PWID tend to have fluctuant engagement in HR, whereas the model continuously accrues these costs over a 30-year period.

As HR expenses are currently met through external donor funding in SSA, we considered their exclusion as part of the sensitivity analysis. This resulted in a substantial reduction in the overall cost of interventions and yielded improved cost-effectiveness universally. However, these resources are finite and future projects are likely to in-part require government support, particularly when considering expanded coverage (Harm Reduction International, 2018). It is of further interest to note that the preferred choice of HR is OST despite being significantly more expensive (OST; $USD 972 versus NSP; $USD 150 per PWID annually) (Wilson, 2014). This selective HR practice is commonplace across SSA and reflects a wider societal and cultural challenge to delivering combined HR (Harm Reduction International, 2018). Thus, targeting a reduction in the cost of OST and increasing the provision for NSP may prove to be useful methods for national bodies attempting to shape a sustainable future HR policy in resource-limited settings.

There is also a modest investment required to improve screening in this model. Levels of screening in the base-case are minimal and are limited to HCV antibody screening

only, reflecting the wider problem of under-testing in LMIC-settings, where 80% of cases remain undiagnosed (World Health Organisation, 2018b). Consequently, screening costs are negligible (USD$276 annually) in the base-case. Recent advances in HCV diagnostics make the confirmation of viraemia not only cost-amenable but also technically feasible. We have recently validated the performance of the Xpert® HCV FS VL and HCVcAg DBS among PWID in Dar-es-Salaam (Mohamed et al., 2020; Mohamed et al., 2017). The annual cost of screening increased to USD$2,816 in strategy B, reflecting the added cost of viraemia confirmation. In strategy C increased screening costs (USD$9,844 annually) are driven by the increased proportion of PWID screened and also the need for Xpert® confirmation of HCVcAg DBS negative cases to avoid false negatives. Recent work by Lamoury and colleagues has shown that improved sensitivity of HCVcAg DBS testing (88.6%) (Lamoury et al., 2018), which may reduce the cost of duplicated testing and simplify the diagnostic algorithm in strategy C, improved retention along the cascade-of-care in community PWID screening.

In terms of treatment related costs, the advent of generic DAAs has dramatically brought down treatment costs to as low as USD$50, an affordable price in the low-income context (Hill, Simmons, Gotham, & Fortunak, 2016). In our setting, the use of generic treatment resulted in an overall cost of USD$80,880-160,440 over a thirty-year period. In addition, their minimal side effect profile and high efficacy potentially enables the simplification of follow-up to two visits; end of treatment and SVR12. Even with lower SVR rates, as seen in the genotype 4r sub-population in Rwanda (Gupta et al., 2019), there does not seem to be a significant impact on the overall value of our treatment strategies. Finally, unlike HIV and HBV, the HCV therapy is finite (two-to-

three months) and consequently any associated costs would be front-loaded during programmatic scale-up.

It is also important to consider that screening and treatment costs are incurred upfront, making them less attractive from a healthcare payer's perspective. In comparison, prospective HCV disease-related costs take time to accrue. These are minimal for disease states up to compensated cirrhosis (an average of USD$ 38-90 per person per annum), but the annual management of liver disease complications (DC and HCC) are estimated to exceed USD$ 1,000 in Tanzania (Chatwal, 2019). Over a 30-year period there is a worrying change in the profile of liver disease among untreated individuals (Supplementary figure 2a-b) only a minority experience complications. As it is this sub-population with disease complications that incur the most significant disease-related costs, it is understandable that such costs projected in the model are similar across all strategies.

One possible approach to minimising healthcare provider costs rests with synergising resources with established public health programmes, such as those related to HIV and TB consistent with universal health coverage approach (The Global Fund, 2019). In our case, the existing OST clinic is supported by US PEPFAR where we have successfully integrated on-site Xpert® HCV viral load testing into existing services provided by the central TB reference laboratory (Mohamed et al., 2020). In spite of the clear benefits from pooling resources from existing initiatives, there is a growing concern for the longevity of these programmes particularly as they are heavily dependent on external donor funding (Albert et al., 2016; Global State of Harm Reduction, 2018). For example in 2015 government contribution to HIV care in

Tanzania amounted to 2% of the total expenditure (Resch, Ryckman, & Hecht, 2015). In addition to increasing governmental responsibility, alternative funding sources, such as through bond initiatives and independent co-payment schemes, have been proposed to safeguard and expand existing programmes (Kakaire, Schlech, Coutinho, Brough, & Parkes-Ratanshi, 2016; Resch et al., 2015).

We recognise that our model has some limitations. First, it is not dynamic and therefore does not account for the effect of interventions on disease incidence over time. However, the importance of existing HR has been previously highlighted by Scott and colleagues, who suggested that a withdrawal of all HR services in Tanzania would result in a doubling of HCV incidence by 2030 (Scott et al., 2019). Furthermore, modelling data have reinforced the argument for rapid scale-up of combination HR and HCV treatment for PWID in East Africa, indicating that this could reduce HCV incidence by up to 90% (Stone et al., 2021). These epidemiological modelling findings are complemented by our cost-effectiveness analysis. In particular, it highlights that a sustained modest financial investment is likely to be required in order to support a successful scale-up intervention, which includes improved access to HR.

However, it may be considered somewhat unrealistic to achieve such high levels of screening and treatment by 2030, given access to diagnosis and treatment is currently not readily available. Our model is designed to simulate a more practical means of scaling up screening and treatment within an extremely resource-constraint setting. From an implementation perspective, we have already demonstrated that Xpert® HCV FS VL testing can be seamlessly integrated within the existing service and that synergism with existing infrastructure avoids additional laboratory and instrument-

related costs (Mohamed et al., 2020). While, treatment can be easily monitored as patients attend daily to receive OST. The expansion of a community-based screening programme may be more challenging. The use of DBS would certainly overcome the potential issue of decentralised sample collection, and we have demonstrated that HCVcAg can be performed with reasonable accuracy in this setting (Mohamed et al., 2017). A possible means for initial implementation of this form of screening may be in individuals currently receiving NSP, as this is often delivered by a community support worker. Our results indicate that restricted treatment of PWID engaged in HR resulted in 13.3% of the total PWID population being treated over the 30-year period, while expansion to include community-based treatment resulted in 25.5% coverage. Recent modelling data supports the notion that low coverage of treatment in conjunction with suitable HR can suffice in achieving elimination and avoid further rebound reinfection (Gountas, Sypsa, Blach, Razavi, & Hatzakis, 2018). Although this has generally been reported as low in PWID (1.9-4.6 per 100 person-years), these have all been from well-resourced settings with higher levels of HR (Akiyama et al., 2019; Aspinall et al., 2013; Dore et al., 2016). A more recent meta-analysis of HCV reinfection in resource-limited settings reported a pooled rate of 2.8 per 100-person years (Muller et al., 2020). As reinfection maybe an important consideration in our setting, where HR is limited, we conducted a supplementary cost-effectiveness analysis (Supplementary Table 1), which incorporated a fixed annual rate of reinfection. This resulted in 28.4% of treated individuals being reinfected over a 30-year period. However, only a marginal effect on the ICER per QALY or DALY values for both treatment scenarios is observed (Supplementary Table 1).

However empirical data for reinfection among PWID in Africa are lacking. Thus, we believe that it would be important to conduct a treatment intervention in this setting in order to compare reinfection rates to the existing literature. Second, there is limited description and information of PWID unengaged in HR in our setting. Therefore, we have assumed that the clinical characteristics and disease epidemiology are equivalent to those who are engaged in HR services. Differences in characteristics such as risk-behaviour and proportion of female PWID may underestimate the burden of HCV and progression of liver disease in this more marginalised sub-population. Third, we have assumed progression rates based on meta-analysis which may not reflect a population in SSA. Specifically, the high prevalence of HBV (10%) and untreated HIV infection may under-estimate the rate of liver disease progression (Mohamed et al., 2018). Finally, our study is an assessment from the healthcare payer's perspective and thus, the societal benefits of HCV treatment are not considered. This is particularly important given the young median age of our cohort is 38 years. Therefore, if HCV treatment is considered to form part of societal reintegration then this may result in further economic benefits than those limited to avoiding ill health.

Conclusion

With an established HR programme, Tanzania represents a unique opportunity to progress the agenda for micro-elimination of HCV among PWID in resource-limited settings. Our analysis confirms that strategies to introduce even a modest degree of treatment restricted to PWID engaged in HR is likely to be cost-effective. While, expanded treatment to enrol those not engaged in HR increased treatment uptake, the cost-effectiveness is influenced by implementation costs. Although integration under the umbrella of existing national HIV programmes might alleviate some of the

additional financial burden, the true test remains in securing the funds to safeguard the provision of HR, initiate and sustain HCV screening and treatment in this neglected population.

Conflict of Interest

All authors have no conflict of interest to declare in relation to this study.

Funding and Acknowledgements

This study was supported by an Imperial College Wellcome Trust Centre Global Health Research Seed Grant. In addition, infrastructure support was provided by the Imperial College London NIHR Biomedical Facility.

518 Table 1. Epidemiological, cost and utility model parameters for PWID in Dar-es-
519 Salaam, Tanzania

Epidemiology			
Parameter	*Point estimate*	*Distribution, input upper and lower bounds*	*Reference*
Total PWID*	12,000	Uniform (min 9,600, max 1,440)	(National Aids Control Programme (NACP), 2014)
Total registered in HR*	5,500	Uniform (min 4,400, max 6,600)	(Scott, 2019)
Total actively engaged in HR *, **	2,805	Uniform (min 2,244, max 3,366)	(Mohamed et al., 2018)
Anti-HCV prevalence	31.0%	Uniform (min 21.8%, max 31.0%)	(Mohamed et al., 2018), (Degenhardt et al., 2017)
HCV RNA prevalence***	18.8%	Uniform (min 18.8%, max 23.9)	(Mohamed et al., 2020),
Baseline mild liver disease (F0/F1)	83%	Uniform (min 67%, max 83%)	(Mohamed et al., 2018), (Chatwal, 2019)
Baseline moderate liver disease (F2/F3)	12%	Uniform (min 12%, max 25%)	(Mohamed et al., 2018), (Chatwal, 2019)
Baseline compensated cirrhosis	5%	Uniform (min 5%, max 8%)	(Mohamed et al., 2018), (Chatwal, 2019)
DAA treatment SVR rate	95%	Uniform (min 87%, max 95%)	(Dore et al., 2016; Grebely et al., 2018), (Gupta et al., 2019)
Annual F0 to F1	0.128	Uniform (min 0.080, max 0.176)	(Smith et al., 2015)
Annual F1 to F2	0.059	Uniform (min 0.035, max 0.082)	(Smith et al., 2015)
Annual F2 to F3	0.078	Uniform (min 0.056, max 0.100)	(Smith et al., 2015)
Annual F3 to Cirrhosis	0.116	Uniform (min 0.070, max 0.161)	(Smith et al., 2015)
Annual Cirrhosis to Decompensation (DC)	0.0018	Uniform (min 0.0003, max 0.0033)	(Smith et al., 2015)
Annual Cirrhosis to Hepatocellular carcinoma (HCC)	0.0003	Uniform (min 0.0001, max 0.0006)	(Smith et al., 2015)
Annual DC to HCC	0.014	Uniform (min 0.014, max 0.068	(Smith et al., 2015), (Planas et al., 2004)

Annual DC to death	0.130	Uniform (min 0.111, max 0.150	(Shepherd et al., 2007), (Fattovich et al., 1997)
Annual HCC to death	0.430	Uniform (min 0.370, max 0,482)	(Shepherd et al., 2007), (Fattovich et al., 1997)
Annual Background mortality	0.0145	Uniform (min 0.01 to 0.019)	(Mathers et al., 2013)
Annual Reinfection rate	0.028	Uniform min 0, max 10.5	(Muller et al., 2020)
Costs (USD$)			
Anti-HCV	1.50	Uniform (min 1, max 5)	(World Health Organisation, 2018a)
Xpert® HCV VL	14.90	Uniform (min 10, max 200)	(Mohamed et al., 2020), max estimation based on conventional HCV RNA cost
HCV core Ag DBS	16	Uniform (min 10, max 200)	max estimation based on conventional HCV RNA cost
Clinical assessment	100	Uniform (min 80, max 120)	Based on local estimate
Outreach assessment*	25	Uniform (min 20, max 30)	(Meehan et al., 2017)
Harm Reduction OST (90% weighted) NSP (10% weighted)	 972 150	Uniform (min 0, max 1,000)	 (Wilson, 2014) (Medecins Du Monde, 2018)
DAA therapy	150	Uniform (min 100, max 1,000)	(Médecins Sans Frontiéres, 2018)
Treatment follow up*	100	Uniform (min 80, max 120)	(Chatwal, 2019)

F0 to F1*	38	Uniform (min 30, max 46)	(Chatwal, 2019)
F2 to F3*	77	Uniform (min 62, max 92)	(Chatwal, 2019)
Cirrhosis*	90	Uniform (min 72, max 108)	(Chatwal, 2019)
DC*	1002	Uniform (min 801, max 1202)	(Chatwal, 2019)
HCC*	1842	Uniform (min 1474, max 2210)	(Chatwal, 2019)
Utilities (QALYs)			
Uninfected/spontaneous clearance	0.94	Uniform (min 0.94, max 1.0)	(Martin et al., 2016)
Untreated F0 to F1*	0.77	Uniform (min 0.62, max 0.77)	(Shepherd et al., 2007; Wright et al., 2006), (Han, Francois, & Toumi, 2021)
Untreated F2 to F3*	0.66	Uniform (min 0.53, max 0.66)	(Shepherd et al., 2007; Wright et al., 2006), (Han et al., 2021)
Untreated Cirrhosis*	0.55	Uniform (min 0.44, max 0.55)	(Shepherd et al., 2007; Wright et al., 2006), (Han et al., 2021)
Untreated DC*	0.45	Uniform (min 0.36, max 0.45)	(Shepherd et al., 2007; Wright et al., 2006), (Han et al., 2021)
Untreated HCC*	0.45	Uniform (min 0.38, max 0.45)	(Shepherd et al., 2007; Wright et al., 2006), (Han et al., 2021)

Treated F0 to F1*	0.82	Uniform (min 0.77, max (0.98)	(Shepherd et al., 2007; Wright et al., 2006)
Treated F2 to F3*	0.72	Uniform (min 0.66, max 0.86)	(Shepherd et al., 2007; Wright et al., 2006)
Treated Cirrhosis*	0.61	Uniform (min 0.55, max 0.73)	(Hartwell, Jones, Baxter, & Shepherd, 2011)
Utilities (DALYs)			
Uninfected/spontaneous clearance	0	-	(Stanaway et al., 2016), (Salomon et al., 2015)
Treated/Untreated F0 to F4	0	Uniform (min 0, max 0.1)	(Stanaway et al., 2016), (Salomon et al., 2015) max value based on estimation
Treated/Untreated DC	0.178	Uniform (min 0.123, max 0.250)	(Stanaway et al., 2016), (Salomon et al., 2015)
Treated/Untreated HCC	0.451	Uniform (min 0.307, max 0.600)	(Stanaway et al., 2016), (Salomon et al., 2015)

520

521

522 * *Parameters varied by 20% for both deterministic and probabilistic sensitivity analysis*

523 ** *Calculated as 51% of the total PWID population enrolled in HR*

524 *** *Calculated on basis that 61-77% of anti-HCV positive PWID are HCV RNA positive*

525

526 Table 2. Summary of interventional strategies stratified by engagement in harm
527 reduction

PWID (n=12,000)		
Strategies	**Harm Reduction (HR)** **(n= 5,500, (44%))**	**No HR** **(n= 6,500, (56%))**
A: Status Quo	• All patients screened for anti-HCV, no further assessment and treatment	• No intervention
B: Scale-up treatment in HR only	• All patients screened for anti-HCV • 51% 'active attenders' • 74% of 'active attenders' linked to care (POC viral load assessment) • 80% HCV RNA positive treated with DAAs • 95% SVR	• No intervention
C: Scale-up treatment in all PWID	• As in 'Strategy B'	• '*Outreach screening':* 50% HCV core Antigen DBS* • 50% HCV RNA positive treated with DAAs • 95% SVR

528

529 ** All HCVcAg negative samples undergo further Xpert® HCV viral load confirmation*

530 *All screening and treatment is undertaken in the first model cycle*

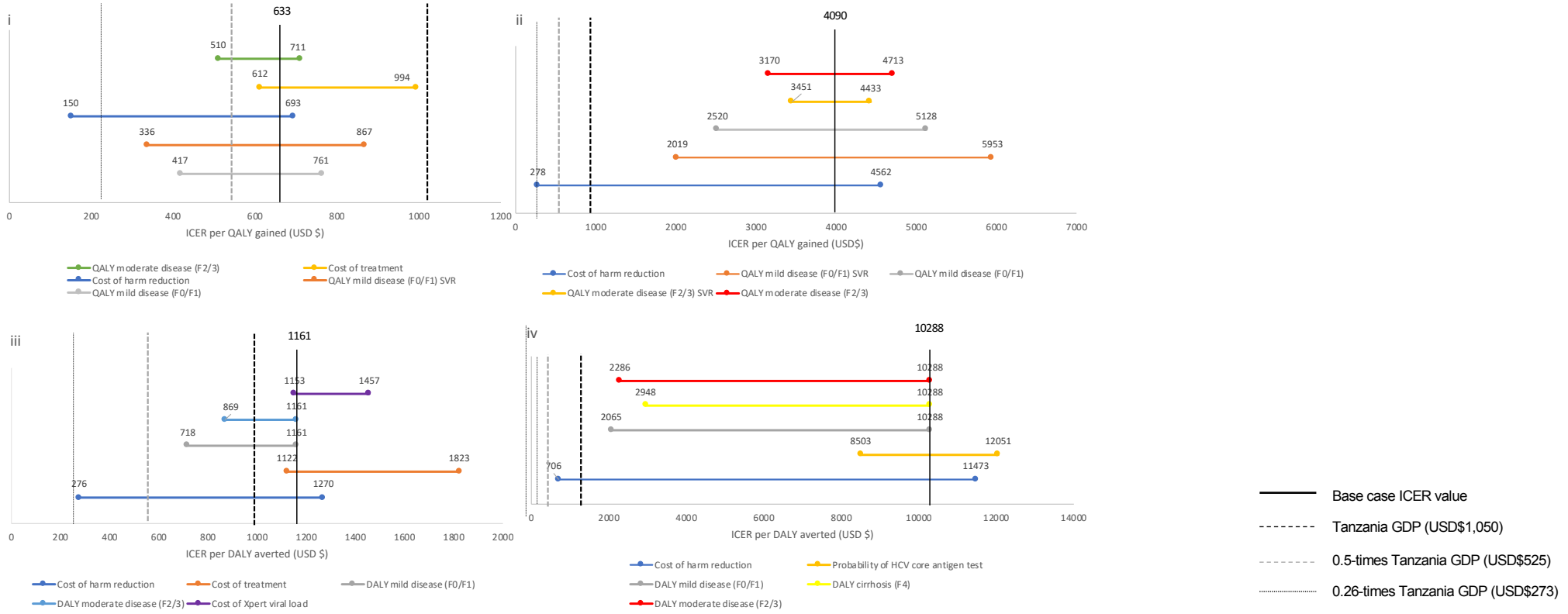
531

532 Table 3. Model outputs for cost, utility and ICER for each strategy when compared to status-quo

Strategy	Total Cost per PWID ($)	Per PWID screening cost (USD$)	Per PWID Treatment cost (USD$)	Per PWID disease cost (USD$)	Per PWID harm reduction cost (USD$)	Per PWID QALY	Per PWID DALY	ICER (USD$) per QALY gained	ICER (USD$) per DALY averted	Total PWID treated (n)
A: Status Quo	1,736.32	0.69	0	179.46	1,556.17	2.87	3.84	-	-	0
B: Scale-up treatment in HR only	1,776.54	7.04	6.74	175.92	1,586.84	2.93	3.83	633.42	1,161.23	293
C: Scale-up treatment in all PWID	2,163.04	24.61	13.37	171.12	1,953.94	2.97	3.80	4,090.87	10,288.42	575

533

Figure 1i-iv. Parameters with highest variability in univariable sensitivity analysis when comparing scenario A (status quo) with: (i) scenario B (screening and treatment in harm reduction settings) using cost per QALY gained, (ii) scenario C (screening and treatment in harm reduction and community settings) using cost per QALY gained, (iii) scenario B using cost per DALY averted and (iv) scenario C using cost per DALY averted.



Variables presented are those with the largest influence on the ICER value for each respective scenario. All variables were included in the DSA (please refer to Table 1 for a upper and lower bounds and references).

Figure 2a. Monte Carlo simulation cost-effectiveness acceptability curve with transition points marked for ICER per QALY values where Strategy B and C become dominant.

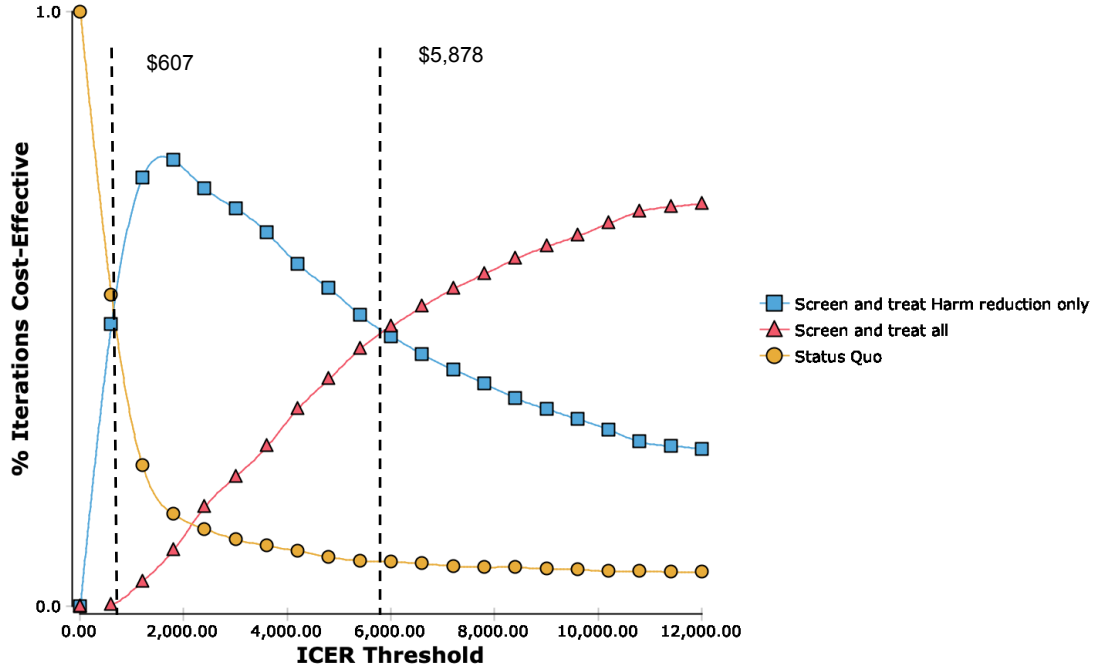
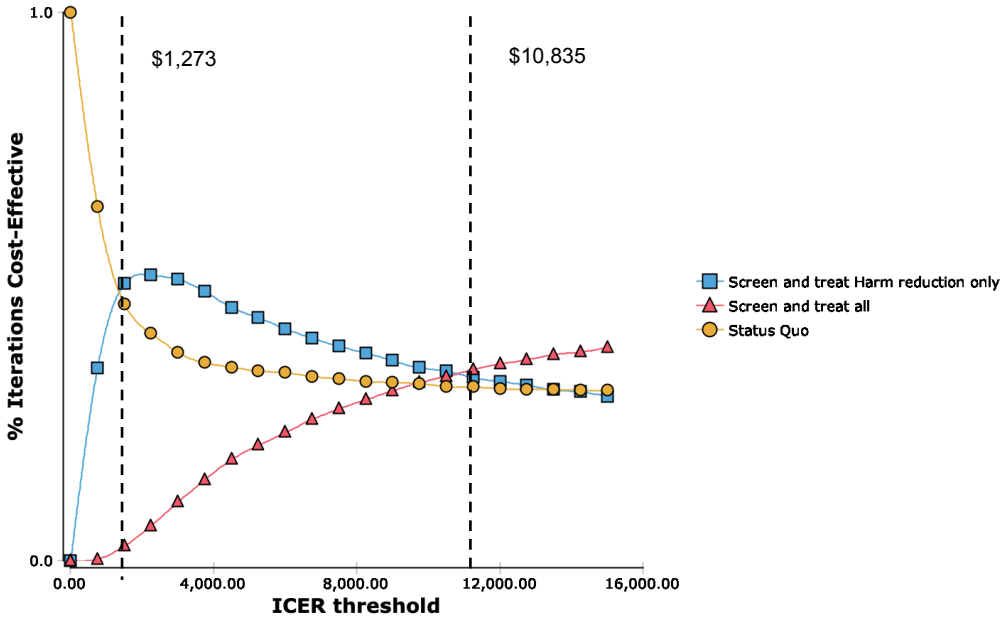


Figure 2b. Monte Carlo simulation cost-effectiveness acceptability curve with transition points marked for ICER per DALY values where Strategy B and C become dominant.



References

Akiyama, M. J., Lipsey, D., Heo, M., Agyemang, L., Norton, B. L., Hidalgo, J., . . . Litwin, A. H. (2019). Low Hepatitis C Reinfection Following Direct-Acting Antiviral Therapy Among People Who Inject Drugs on Opioid Agonist Therapy. *Clin Infect Dis*. doi:10.1093/cid/ciz693

Albert, H., Nathavitharana, R. R., Isaacs, C., Pai, M., Denkinger, C. M., & Boehme, C. C. (2016). Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: what lessons have we learnt and how can we do better? *Eur Respir J, 48*(2), 516-525. doi:10.1183/13993003.00543-2016

Aspinall, E. J., Corson, S., Doyle, J. S., Grebely, J., Hutchinson, S. J., Dore, G. J., . . . Hellard, M. E. (2013). Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis, 57 Suppl 2*, S80-89. doi:10.1093/cid/cit306

Boyer, S., Baudoin, M., Woode, ME., Mardan, G., Lemoine, M., Sylla, B., Kouanfack, P., Carrieri, P., Rouveau, N., Moh, R., Seydi,M., Attia, A., Lacombe, K. (2018). Cost-effectiveness of Sofosbuvir-based hepatitis C regimens in Central and West Africa (ANRS 12342). *EASL, 68*, S184-S185.

Chatwal, J. (2019). Hep C Calculator. Retrieved from https://www.hepccalculator.org/hepccalc

Chhatwal, J., Chen, Q., Bethea, E. D., Ladd, M. A., Mueller, P. P., Hutin, Y., & Aggarwal, R. (2018). Hep C Calculator: an online tool for cost-effectiveness analysis of DAAs. *Lancet Gastroenterol Hepatol, 3*(12), 819. doi:10.1016/S2468-1253(18)30281-4

Degenhardt, L., Charlson, F., Stanaway, J., Larney, S., Alexander, L. T., Hickman, M., . . . Vos, T. (2016). Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the Global Burden of Disease Study 2013. *Lancet Infect Dis, 16*(12), 1385-1398. doi:10.1016/S1473-3099(16)30325-5

Degenhardt, L., Peacock, A., Colledge, S., Leung, J., Grebely, J., Vickerman, P., . . . Larney, S. (2017). Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Health, 5*(12), e1192-e1207. doi:10.1016/S2214-109X(17)30375-3

Dore, G. J., Altice, F., Litwin, A. H., Dalgard, O., Gane, E. J., Shibolet, O., . . . Group, C. E. C.-S. S. (2016). Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Ann Intern Med, 165*(9), 625-634. doi:10.7326/M16-0816

Fattovich, G., Giustina, G., Degos, F., Tremolada, F., Diodati, G., Almasio, P., . . . Realdi, G. (1997). Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology, 112*(2), 463-472. doi:10.1053/gast.1997.v112.pm9024300

Global State of Harm Reduction. (2018). *Global State of Harm Reduction 6th Edition*. Retrieved from https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf

Gountas, I., Sypsa, V., Blach, S., Razavi, H., & Hatzakis, A. (2018). HCV elimination among people who inject drugs. Modelling pre- and post-WHO elimination era. *PLoS One, 13*(8), e0202109. doi:10.1371/journal.pone.0202109

Grebely, J., Dalgard, O., Conway, B., Cunningham, E. B., Bruggmann, P., Hajarizadeh, B., . . . Group, S. S. (2018). Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterol Hepatol, 3*(3), 153-161. doi:10.1016/S2468-1253(17)30404-1

Gupta, N., Mbituyumuremyi, A., Kabahizi, J., Ntaganda, F., Muvunyi, C. M., Shumbusho, F., . . . Grant, P. M. (2019). Treatment of chronic hepatitis C virus infection in Rwanda with ledipasvir-sofosbuvir (SHARED): a single-arm trial. *Lancet Gastroenterol Hepatol, 4*(2), 119-126. doi:10.1016/S2468-1253(18)30382-0

Han, R., Francois, C., & Toumi, M. (2021). Systematic Review of Health State Utility Values Used in European Pharmacoeconomic Evaluations for Chronic Hepatitis C: Impact on Cost-Effectiveness Results. *Appl Health Econ Health Policy, 19*(1), 29-44. doi:10.1007/s40258-020-00600-w

Harm Reduction International. (2018). *The Global State of Harm Reduction*. Retrieved from https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf

Hartwell, D., Jones, J., Baxter, L., & Shepherd, J. (2011). Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess, 15*(17), i-xii, 1-210. doi:10.3310/hta15170

Hecht, R., Hiebert, L., Spearman, W. C., Sonderup, M. W., Guthrie, T., Hallett, T. B., . . . Resch, S. (2018). The investment case for hepatitis B and C in South Africa: adaptation and innovation in policy analysis for disease program scale-up. *Health Policy Plan, 33*(4), 528-538. doi:10.1093/heapol/czy018

Heffernan, A., Cooke, G. S., Nayagam, S., Thursz, M., & Hallett, T. B. (2019). Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *Lancet, 393*(10178), 1319-1329. doi:10.1016/S0140-6736(18)32277-3

Hill, A., Simmons, B., Gotham, D., & Fortunak, J. (2016). Rapid reductions in prices for generic sofosbuvir and daclatasvir to treat hepatitis C. *J Virus Erad, 2*(1), 28-31. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27482432

Kakaire, T., Schlech, W., Coutinho, A., Brough, R., & Parkes-Ratanshi, R. (2016). The future of financing for HIV services in Uganda and the wider sub-Saharan Africa region: should we ask patients to contribute to the cost of their care? *BMC Public Health, 16*, 896. doi:10.1186/s12889-016-3573-0

Kim, D. D., Hutton, D. W., Raouf, A. A., Salama, M., Hablas, A., Seifeldin, I. A., & Soliman, A. S. (2015). Cost-effectiveness model for hepatitis C screening and treatment: Implications for Egypt and other countries with high prevalence. *Glob Public Health, 10*(3), 296-317. doi:10.1080/17441692.2014.984742

Lacombe, K. M., R.; Chazallon, C.; Babacar, S.; Lemoine, M.; Kouanfack, C.; Leuwat, E.; Sida,M; Fadiga, F.; Tagni-Sartre, M.; Attia, A. (2018). TREATMENT OF CHRONIC HEPATITIS C GT1,2,4 IN AFRICA: FINAL RESULTS OF ANRS 12311 TAC TRIAL. *CROI*.

Lamoury, F. M. J., Hajarizadeh, B., Soker, A., Martinez, D., Quek, C., Cunningham, P., . . . Applegate, T. L. (2018). Evaluation of a Hepatitis C Virus Core Antigen Assay in Plasma and Dried Blood Spot Samples. *J Mol Diagn, 20*(5), 621-627. doi:10.1016/j.jmoldx.2018.05.010

Larney, S., Peacock, A., Leung, J., Colledge, S., Hickman, M., Vickerman, P., . . . Degenhardt, L. (2017). Global, regional, and country-level coverage of interventions to prevent and

manage HIV and hepatitis C among people who inject drugs: a systematic review. *Lancet Glob Health, 5*(12), e1208-e1220. doi:10.1016/S2214-109X(17)30373-X

Martin, N. K., Vickerman, P., Brew, I. F., Williamson, J., Miners, A., Irving, W. L., . . . Hickman, M. (2016). Is increased hepatitis C virus case-finding combined with current or 8-week to 12-week direct-acting antiviral therapy cost-effective in UK prisons? A prevention benefit analysis. *Hepatology, 63*(6), 1796-1808. doi:10.1002/hep.28497

Mathers, B. M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L., & Hickman, M. (2013). Mortality among people who inject drugs: a systematic review and meta-analysis. *Bull World Health Organ, 91*(2), 102-123. doi:10.2471/BLT.12.108282

Medecins Du Monde (2018). [Personal communication: cost of NSP].

Médecins Sans Frontiéres. (2018). MSF secures lower price for generic hepatitis C treatment. [Press release]. Retrieved from http://www.msf.org/en/ article/msf-secures-lower-price-generic-hepatitis-c- treatment

Meehan, S. A., Beyers, N., & Burger, R. (2017). Cost analysis of two community-based HIV testing service modalities led by a Non-Governmental Organization in Cape Town, South Africa. *BMC Health Serv Res, 17*(1), 801. doi:10.1186/s12913-017-2760-8

Mohamed, Z., Mbwambo, J., Rwegasha, J., Mgina, N., Doulla, B., Mwakale, P., . . . Lemoine, M. (2020). In-field evaluation of Xpert(R) HCV viral load Fingerstick assay in people who inject drugs in Tanzania. *Liver Int, 40*(3), 514-521. doi:10.1111/liv.14315

Mohamed, Z., Mbwambo, J., Shimakawa, Y., Poiteau, L., Chevaliez, S., Pawlotsky, J. M., . . . Lemoine, M. (2017). Clinical utility of HCV core antigen detection and quantification using serum samples and dried blood spots in people who inject drugs in Dar-es-Salaam, Tanzania. *J Int AIDS Soc, 20*(1), 21856. doi:10.7448/IAS.20.1.21856

Mohamed, Z., Rwegasha, J., Kim, J. U., Shimakawa, Y., Poiteau, L., Chevaliez, S., . . . Lemoine, M. (2018). The hepatitis C cascade of care in people who inject drugs in Dar es Salaam, Tanzania. *J Viral Hepat, 25*(12), 1438-1445. doi:10.1111/jvh.12966

Muller, A., Vlahov, D., Akiyama, M. J., & Kurth, A. (2020). Hepatitis C Reinfection in People Who Inject Drugs in Resource-Limited Countries: A Systematic Review and Analysis. *Int J Environ Res Public Health, 17*(14). doi:10.3390/ijerph17144951

National Aids Control Programme (NACP). (2014). *Consensus estimates on key population size and HIV prevalence in Tanzania*. Retrieved from http://www.healthpolicyproject.com/pubs/391_FORMATTEDTanzaniaKPconsensusmtgreport.pdf. ISBN: 978-9987-650-88-0.

Ochalek, J., Lomas, J., & Claxton, K. (2018). Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health, 3*(6), e000964. doi:10.1136/bmjgh-2018-000964

Ochalek, J. M. L., J.; Claxton K.P. (2015). *Cost per DALY averted thresholds for low- and middle-income countries. evidence from cross country data.* Retrieved from Centre for Health Economics:

Planas, R., Balleste, B., Alvarez, M. A., Rivera, M., Montoliu, S., Galeras, J. A., . . . Sola, R. (2004). Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *J Hepatol, 40*(5), 823-830. doi:10.1016/j.jhep.2004.01.005

Resch, S., Ryckman, T., & Hecht, R. (2015). Funding AIDS programmes in the era of shared responsibility: an analysis of domestic spending in 12 low-income and middle-income countries. *Lancet Glob Health, 3*(1), e52-61. doi:10.1016/S2214-109X(14)70342-0

Salomon, J. A., Haagsma, J. A., Davis, A., de Noordhout, C. M., Polinder, S., Havelaar, A. H., . . . Vos, T. (2015). Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health, 3*(11), e712-723. doi:10.1016/S2214-109X(15)00069-8

Scott, N. (2019). upscaling prevention, testing and treatment to control hepatitis c as a public health threat in Dar es Salaam Tanzania. *International Journal of Drug Policy*.

Scott, N., Mohamed, Z., Rwegasha, J., Mbwambo, J., Lemoine, M., & Hellard, M. (2019). Upscaling prevention, testing and treatment to control hepatitis C as a public health threat in Dar es Salaam, Tanzania: A cost-effectiveness model. *Int J Drug Policy*, 102634. doi:10.1016/j.drugpo.2019.102634

Shepherd, J., Jones, J., Hartwell, D., Davidson, P., Price, A., & Waugh, N. (2007). Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess, 11*(11), 1-205, iii. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17346498

Smith, D. J., Combellick, J., Jordan, A. E., & Hagan, H. (2015). Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): A systematic review and meta-analysis. *Int J Drug Policy, 26*(10), 911-921. doi:10.1016/j.drugpo.2015.07.004

Stanaway, J. D., Flaxman, A. D., Naghavi, M., Fitzmaurice, C., Vos, T., Abubakar, I., . . . Cooke, G. S. (2016). The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet, 388*(10049), 1081-1088. doi:10.1016/S0140-6736(16)30579-7

Stone, J., Fraser, H., Walker, J. G., Mafirakureva, N., Mundia, B., Cleland, C., . . . Vickerman, P. (2021). Modelling the Impact of Prevention and Treatment Interventions on HIV and Hepatitis C Virus Transmission Among People Who Inject Drugs in Kenya. *medRxiv*, 2021.2002.2002.21251008. doi:10.1101/2021.02.02.21251008

Tanzania National AIDS Control Programme. (2014). Consensus estimates on key population size and HIV prevalence in Tanzania. Retrieved from https://www.healthpolicyproject.com/pubs/391_FORMATTEDTanzaniaKPconsensusmtgreport.pdf

The Global Fund. (2019). *Focus on universal health coverage*. Retrieved from https://www.theglobalfund.org/media/5913/publication_universalhealthcoverage_focuson_en.pdf?u=637146787950000000

Thein, H. H., Yi, Q., Dore, G. J., & Krahn, M. D. (2008). Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology, 48*(2), 418-431. doi:10.1002/hep.22375

Trickey, A., Fraser, H., Lim, A. G., Peacock, A., Colledge, S., Walker, J. G., . . . Vickerman, P. (2019). The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *Lancet Gastroenterol Hepatol, 4*(6), 435-444. doi:10.1016/S2468-1253(19)30085-8

Uchtenhagen, A. (2004). Substance use problems in developing countries. *Bull World Health Organ, 82*(9), 641. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15628199

Wilson, D. (2014). *Cost-effectiveness of harm reduction.* Paper presented at the UNODC Scientific Event, Vienna, Austria.

World Health Organisation. (2003). *WHO guide to cost-effectiveness analysis*. Retrieved from https://www.who.int/choice/publications/p_2003_generalised_cea.pdf?ua=1

World health Organisation. (2016). Global health sector strategy on viral hepatitis 2016-2021. Retrieved from http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/

World Health Organisation. (2018a). *PROGRESS REPORT ON ACCESS TO HEPATITIS C TREATMENT*. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/260445/WHO-CDS-HIV-18.4-eng.pdf?sequence=1

World Health Organisation. (2018b). Progress report on access to hepatitis C treatment Focus on overcoming barriers in low- and middle-income countries. Retrieved from https://www.who.int/hepatitis/publications/hep-c-access-report-2018/en/

Wright, M., Grieve, R., Roberts, J., Main, J., Thomas, H. C., & Investigators, U. K. M. H. C. T. (2006). Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess, 10*(21), 1-113, iii. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16750059