

1 Generating Synthetic Multi-national Longitudinal 2 Cohorts for Clinically Grounded HIV Research

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22 ABSTRACT

High-quality, widely accessible international longitudinal cohort data for people living with HIV (PWH) have long been needed for advancing open science and data-driven innovation, yet stringent and incongruent privacy regulations have made data sharing difficult. Synthetic data generation offers a promising privacy-preserving alternative, but producing realistic synthetic cohorts of PWH remains challenging due to complex temporal dynamics, interdependent clinical variables, long follow-up periods, and high missingness inherent in such data. Here, we introduce Medical Longitudinal latent Diffusion (MeLD), a generative model designed to synthesize variable-length, decades-spanning, mixed-type clinical trajectories with missingness.
Using the Caribbean, Central, and South America Network for HIV Epidemiology (CCASAnet) cohort, one of the world's largest international HIV datasets with over 30 years of follow-up on nearly 50,000 PWH, we show that MeLD consistently outperforms state-of-the-art methods across data utility, fidelity, and privacy. Notably, MeLD excels in longitudinal inference utility, accurately reproducing time-to-death estimates and risk factor effects, while maintaining strong privacy protection. This work delivers the first in-depth, large-scale, and openly accessible synthetic longitudinal cohort of PWH that faithfully preserves the distributional patterns and clinical associations observed in real data, offering an immediately deployable resource for hypothesis generation, methods innovation, medical training, and reproducible HIV research.

24 Introduction

Longitudinal clinical cohort data are invaluable for tracking the evolving needs and outcomes of individuals with chronic conditions. For people living with HIV (PWH), long-term clinical cohorts have been central to major advances in treatment development and epidemiological surveillance¹. Continued progress in these areas hinges on the ability to share rich, individual-level clinical trajectories collected from diverse global sources. However, stringent and incongruent privacy regulations, ranging from the European Union's General Data Protection Regulation (GDPR) to Brazil's Lei Geral de Proteção de Dados (LGPD), have erected a patchwork of firewalls that hinder data sharing². Even the most successful international research consortia approve only a handful of narrowly scoped data requests each year, slowing knowledge discovery and dissemination, and ultimately delaying clinical benefits.

Synthetic health data have emerged as a promising way to enable data sharing and collaboration across countries. When generated properly, synthetic data can mimic the statistical properties of source databases without linking produced records

35 to real people, offering a pragmatic path to easier data sharing that preserves privacy^{3–6}. Generative AI technologies have
36 made it possible to produce realistic cross-sectional snapshots of electronic health record (EHR) data⁷ and simple longitudinal
37 sequences⁸, enabling critical applications, such as trial-based association studies⁹, outcome predictive modeling^{10,11}, geotem-
38 poral epidemic forecasting¹², and DNA-disease association analysis¹³—while researchers navigate complex administrative
39 processes required to access real data.

40 However, generating high-quality synthetic longitudinal clinical cohort data faces non-trivial challenges. Cohorts of people
41 with chronic conditions like HIV typically span decades and include critical time-to-event outcomes, such as a variety of
42 clinical endpoints (e.g., diagnoses of comorbidities), medication changes, treatment failures, and mortality. These complexities
43 are fundamental to ensuring clinical relevance and usability of longitudinal data. Yet current synthetic data generation methods
44 struggle to capture the temporal depth and clinical complexity of chronic condition trajectories. Most of these methods are
45 developed and evaluated with short horizons (e.g., 24-hour ICU streams or datasets with a limited number of visits⁸), which
46 can reduce a marathon-length chronic condition journey to a snapshot. Another challenge arises from the need to process
47 and generate a mix of continuous (e.g., HIV viral load measurements), discrete (e.g., test frequencies), and categorical (e.g.,
48 diagnostic codes) variables, while simultaneously preserving their temporal relationships. Existing methods, mostly adapted
49 from unimodal domains like imaging or natural language processing, rely on tokenizing continuous and discrete values into
50 coarse categories. This process potentially obscures clinically meaningful variations¹⁴. Additionally, current synthetic data
51 evaluation strategies typically rely on generic resemblance metrics¹⁵. These are limited in scope. Specially, they do not assess
52 whether scientifically relevant relationships are preserved in synthetic cohort data, which would be a far more demanding
53 standard of data quality. For instance, an essential but missing metric is whether models fitted on synthetic data can reproduce
54 time-to-event patterns observed in real cohorts, an outcome that reflects the analytical value of longitudinal clinical cohort data
55 and is essential for evaluating treatment effects and informing health policy. Another overlooked metric examines whether
56 longitudinal synthetic data can yield risk factor estimates comparable to those derived from real data, which addresses the
57 capability of synthetic data to support scientific hypothesis generation.

58 To address these challenges, we introduce **Medical Longitudinal latent Diffusion** (MeLD), a longitudinal latent diffusion
59 model built on a transformer backbone (Fig. 1). At a high level, MeLD first embeds variables of mixed types into a continuous
60 latent space via a variational autoencoder (VAE), which naturally preserves numerical precision and handles inter-visit time
61 gaps. A transformer-powered diffusion process then learns dependencies across timescales, ranging from short-term oscillations
62 in laboratory measurements to multi-decade survival trends within the latent representations. We complement MeLD with
63 evaluation metrics that jointly assess data utility, fidelity, and privacy, with particular emphasis on time-to-event analysis
64 integrity and risk factor reproducibility.

65 We demonstrate MeLD by generating the first large-scale, shareable, longitudinal synthetic cohort of PWH based on
66 the Caribbean, Central, and South America network for HIV Epidemiology (CCASAnet) cohort^{16,17}, which is part of the
67 International epidemiological Databases to Evaluate AIDS (IeDEA) network—the world’s largest HIV research consortia.
68 The CCASAnet data used in this study pool longitudinal medical records and routinely collected data to track approximately
69 50,000 PWH across six countries, with follow-up spanning over 30 years. Systematic assessment demonstrates that MeLD
70 produces synthetic cohort of PWH that closely mirror the real records across data utility and fidelity metrics, outperforming
71 state-of-the-art generative methods, while remaining robust to standard privacy inference. Notably, MeLD achieves superior
72 performance in preserving long-term time-to-event patterns and risk factors for mortality and clinical endpoints seen in real
73 records. The shareable synthetic replica of the CCASAnet cohort represents a significant step forward in enabling HIV data
74 sharing and opens new avenues to generate meaningful insights that can drive HIV-focused training, education, research, and
75 real-world applications.

76 Results

77 An overview of MeLD and experimental setup

78 *Longitudinal clinical cohort data*

79 This study relies on CCASAnet, a U.S. National Institutes of Health (NIH)-funded multi-country consortium that harmonizes
80 routine clinical care data from HIV clinics in Argentina, Brazil, Chile, Haiti, Honduras, Mexico, and Peru. As of December
81 2024, the cohort (excluding those from Peru) comprises 49,606 adults (≥ 18 years) living with HIV. The CCASAnet database,
82 like those of many chronic condition cohorts, follows a normalized, relational design. Immutable variables (e.g., demographics)
83 sit in cross-sectional tables, whereas time-varying data (e.g., timestamped visits, laboratory results including CD4 cell count
84 and HIV viral load measurement, medications including antiretroviral therapy regimens with start and stop dates, and clinical
85 diagnoses) are in longitudinal tables. This structure is common because it mitigates redundancy, allows incremental updates,
86 and enables analysts to assemble cohorts by joining relevant tables. However, raw data require systematic preprocessing to be
87 suitable for model fitting. To enable longitudinal modeling for synthetic data generation, we reorganize the CCASAnet data

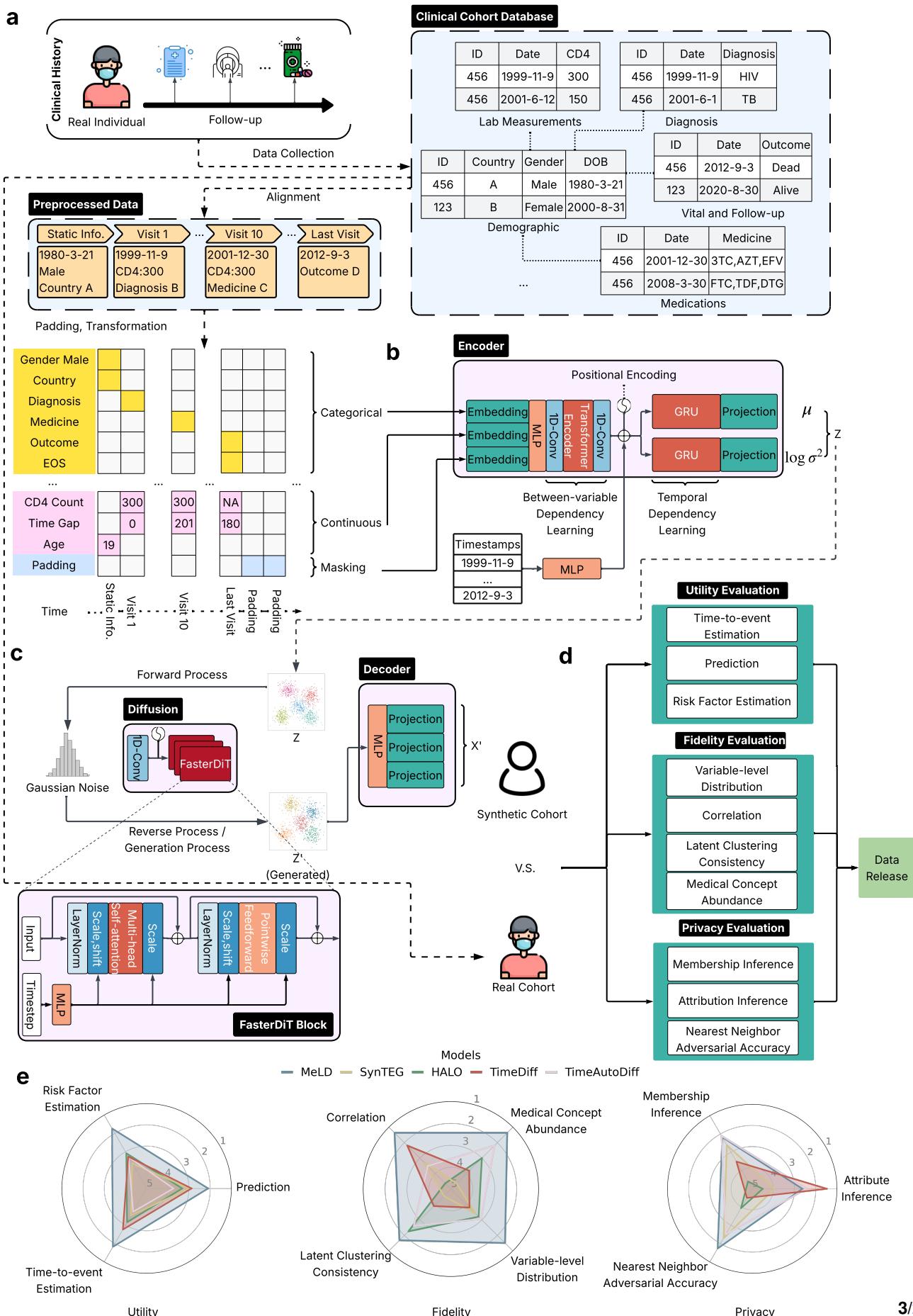


Figure 1. Caption in next page.

Figure 1. An overview of the MeLD architecture, data quality evaluation framework, and corresponding overall model rankings. **a**, Individual-level information from demographics, vital and follow-up status, visits, laboratory results, medications, and diagnoses is time-aligned and structured into a visit-centric sequence, then padded to create AI-ready data. **b**, Visit-level clinical trajectories, containing mixed continuous and categorical fields, are embedded, projected, then passed to a VAE encoder to produce their latent representations. **c**, A DiT-based diffusion module generates synthetic clinical trajectories in the latent space by sampling from Gaussian noise, which are then decoded by the VAE decoder back into the original data space, yielding realistic longitudinal records of variable length. **d**, The resulting synthetic data undergo systematic evaluation across data utility, fidelity, and privacy assessment prior to release. **e**, Ranks of MeLD across data utility, fidelity, and privacy, compared to state-of-the-art synthetic longitudinal data generation methods. Model rankings in each dimension are derived across ten synthetic datasets, generated by two independently trained models, with five datasets generated from each. Smaller values in ranks correspond to higher performance. VAE=variational auto-encoder; MLP=multi-layer perceptron; DiT=diffusion transformer; GRU=gated recurrent units.

88 into a visit-centric format, where longitudinal data are grouped by clinical visits. To balance comprehensive coverage with
89 computational feasibility, we retain up to 120 visits per person, corresponding to the 90th percentile and approximately 36 years
90 of maximum follow-up. Inter-visit time gaps are derived and added as a continuous variable. The resulting real analytic dataset
91 averages 45 visits per person and includes 135 variables. Full details of the datasets are provided in the Methods Section.

92 **Architectural design of MeLD**

93 After assembling longitudinal records into visit-level sequences prefixed by demographic information, an end-of-sequence
94 (EOS) token is appended to each person's final visit. Right-padding is applied with zero-filled pseudo-visits up to a fixed
95 horizon (Fig. 1a). The resulting data preserve chronological order and data type heterogeneity while matching the fixed-size
96 input expected by the encoder of MeLD. Two binary mask sequences with the same length as the constructed data are then
97 created: one flags padded pseudo-visits, the other flags missing values. See the Methods Section for data preprocessing details.

98 MeLD adopts a latent diffusion architecture, in which a VAE translates visit-level representations between the original
99 and latent spaces (Fig. 1b,c). Within the latent space, a diffusion model generates synthetic visit sequences, avoiding the
100 complexity of handling diverse data types in the original space (Fig. 1c). Specifically, the VAE encoder of MeLD first
101 embeds categorical values, continuous values, and data masks (from missing data and padded pseudo-visits), into their own
102 representations using stream-specific embedding modules. At each visit, these embeddings are concatenated and fused through
103 a multi-layer perceptron (MLP) to form a unified representation. To capture the fine-grained associations across variables,
104 we apply multi-channel 1D-convolutions before and after a transformer encoder that models variable-wise dependencies¹⁸.
105 Temporal dynamics across visits are then modeled and aligned using two additional gated recurrent units (GRU), conditioned
106 on embedded timestamps. The output of the VAE encoder is a sequence of temporally aligned visit-level latent representations
107 that serves as the foundation for the subsequent diffusion process, enabling realistic and coherent synthesis of longitudinal
108 records. These representations are parameterized by the mean (μ) and variance (σ^2) of the posterior distribution of each
109 person's underlying clinical trajectory in the latent space.

110 MeLD adopts diffusion transformer (DiT)¹⁹ as its generative backbone, a state-of-the-art algorithm developed for synthetic
111 image generation that replaces the traditional U-Net architecture with a stack of transformer blocks. For longitudinal clinical
112 visit sequences, we adapt DiT by representing each latent visit as a token and performing denoising entirely in the latent space.
113 Gaussian noise is progressively removed from lower-quality visit sequences using self-attention blocks, allowing the model to
114 generate entire clinical trajectories simultaneously at each denoising step, rather than performing autoregressive generation. To
115 address the notoriously long training cycles of standard diffusion, we integrate the FasterDiT acceleration scheme²⁰, which
116 refines training supervision by guiding the model to match both the size and the direction of each denoising velocity step to
117 improve convergence speed. In the generation stage, synthetic clinical visit sequences are produced in the latent space by
118 iteratively denoising Gaussian noise into realistic trajectories.

119 MeLD reconstructs synthetic longitudinal records by decoding the denoised latent sequences using the VAE decoder
120 composed of stacked MLP layers. Finally, three independent projection modules map the decoded sequences into categorical,
121 continuous, and mask fields (missing and EOS masks). We then convert these sequences to the original data format.

122 **Experimental setup**

123 We conduct evaluations at two levels. First, we benchmark MeLD against representative state-of-the-art longitudinal clinical
124 data generators, including models based on generative adversarial network (GANs), language models, diffusion, and latent
125 diffusion. Second, we compare standard MeLD with its variants that swap in alternative diffusion and VAE architectures to
126 assess the impact of MeLD design choices on overall data quality. Specifically, we include the following models:

- 127 1. SynTEG²¹: This model generates timestamped diagnosis sequences through a two-stage process that decouples temporal
128 modeling from visit generation. In the first stage, a recurrent neural network models visit-level dynamics and temporal
129 dependencies in real data by jointly predicting the diagnoses at the next visit and the inter-visit time interval. In the
130 second stage, the hidden states learned from the temporal model serve as the condition of a Wasserstein GAN, which
131 samples the multivariate distribution of diagnoses for each visit. SynTEG does not natively support mixed-type data, so
132 we discretize continuous variables into quantile-based bins, convert them into categorical representations for generation,
133 and generate synthetic continuous values through uniform sampling within relevant bins.
- 134 2. HALO²²: This is a hierarchical language model that decomposes dependency learning into two levels: a coarse-grained,
135 visit-level module and a fine-grained, code-level module. HALO generates visit representations and variable values
136 within each visit autoregressively until an EOS token is produced. HALO also lacks native support for mixed-type data;
137 continuous variables are discretized for training and later generated through sampling using the approach described above
138 for SynTEG.
- 139 3. TimeDiff⁸: This model separately performs Gaussian diffusion for continuous variables and multinomial diffusion for
140 categorical variables, both in the original space. A time-conditioned bi-directional long short-term memory (LSTM)
141 network parameterizes the diffusion process, capturing sequence dynamics in one pass, rather than autoregressively.
142 Since TimeDiff is not designed to generate variable-length sequences, we determine the endpoint of each generate
143 sequence based on the occurrence of death or censoring.
- 144 4. TimeAutoDiff²³: This model uses a latent diffusion architecture with a two-stage training process similar to MeLD.
145 In the first stage, a VAE is trained to project full-length clinical visit sequences between the original mixed-type data
146 space and the latent space. In the second stage, an LSTM-based denoising diffusion probabilistic model (DDPM)²⁴ is
147 trained to reconstruct latent trajectories from Gaussian noise. Noticeably, real timestamps are used both as conditions
148 for second-stage model training and as the “synthetic” timestamps, which increases vulnerability to privacy intrusions
149 and constrains data diversity. To enable a head-to-head comparison with MeLD, we instruct TimeAutoDiff to generate
150 synthetic inter-visit intervals. TimeAutoDiff also does not have an mechanism for variable-length generations, so like
151 TimeDiff, we use death and censoring as terminal events for each generated sequence.

152 To assess the impact of MeLD’s diffusion module on synthetic data quality, we substitute it with the following alternative
153 diffusion architectures for modeling temporal dependencies, while keeping all other components unchanged: 1) DDPM, a
154 Gaussian diffusion model with a convolutional U-Net denoiser²⁴, 2) LSTM, the recurrent backbone used in TimeAutoDiff,
155 modified by removing real timestamp conditioning to be consistent with MeLD’s design, and 3) DiT, a transformer-based
156 denoiser without the convergence acceleration strategies employed in MeLD¹⁹. We also evaluate the impact of MeLD’s VAE
157 component by comparing it to a model that substitutes both MeLD encoder’s GRU and decoder’s MLP with a transformer. This
158 is to test whether a stronger temporal model can bring significant benefit to synthetic data quality. We refer to these baseline
159 models as MeLD-DDPM, MeLD-LSTM, MeLD-DiT, and MeLD-Transformer, respectively. As MeLD-DiT needs substantially
160 longer time to converge, we constrain its training time to match that of MeLD.

161 We randomly partition the CCASAnet cohort into training (85%) and test sets (15%). Each model is trained twice
162 independently on the training set (i.e., two runs), with five synthetic cohorts generated for each run. This yields ten synthetic
163 datasets, all matching the size of the real training set. These ten datasets are used to estimate the 95% confidence intervals (CI)
164 for evaluation metrics using a normal approximation. Since MeLD is the only model explicitly designed to handle missing
165 data in model training and generation, we impute missing values in the real data beforehand using Multivariate Imputation by
166 Chained Equations (MICE)²⁵, a standard approach in epidemiology research, and perform evaluation against imputed data. For
167 MeLD, missing values in the generated synthetic data are post-processed using the same imputation pipeline applied to the real
168 data for consistency in evaluation.

169 We evaluate the quality of the synthetic data along three complementary dimensions (Fig. 1d): 1) data utility, 2) data fidelity,
170 and 3) privacy risks. Recognizing that existing evaluations overemphasize generic resemblance scores and simple outcome
171 prediction while overlooking whether scientifically meaningful relationships are preserved, we explicitly test if models fitted on
172 synthetic data can recover key longitudinal phenomena that are central to HIV research. In the utility dimension, we investigate
173 the utility of the synthetic data to develop prediction models for clinical endpoint prediction. We then go beyond this standard
174 evaluation and investigate time-to-event analysis and risk factor estimation, considering whether time-to-event relationships
175 and covariate effects observed in the real cohort are reproducible in synthetic data. Data fidelity analyses investigate whether
176 statistical properties of the data are preserved, at the variable-level, individual-level, and across time. This is quantified
177 through variable-level distribution and correlation resemblance, latent clustering consistency, medical concept abundance, and
178 missingness patterns. Finally, we apply standard privacy metrics to gauge the risks in sharing the synthetic data.

179 Data Utility

180 To evaluate data utility, we select key tasks that reflect priorities of the HIV research community and the core value of
181 longitudinal clinical cohorts, including time-to-event estimation, outcome prediction, and risk factor estimation.

182 Time-to-event estimation

183 A generative model must capture both short- and long-term dependencies in real data to produce realistic time-to-event estimates.
184 Unlike common evaluation metrics that focus on individual variables or pairwise relationships, time-to-event estimation relies
185 on derived variables computed from multiple underlying fields, making it more sensitive to compounding errors that can
186 occur in synthetic data. Therefore, accurately reproducing time-to-event curves presents a significantly greater challenge for
187 generative models than matching simple statistics alone. We estimate cumulative hazard functions using the Nelson-Aalen
188 method and quantify Kaplan-Meier distance (KM-D) between synthetic and real data²⁶. Two-sided log-rank tests compare
189 survival functions derived from the real and synthetic data. Synthetic and real training data of the same sample size are
190 compared against real test data to allow comparability of *p*-values. Additionally, we evaluate the maximum follow-up time
191 derived from synthetic datasets.

192 In HIV epidemiology, time from antiretroviral therapy (ART) initiation to death is a central outcome, reflecting treatment
193 efficacy, retention in care, and mortality risk. Fig. 2a-c presents aggregated results across all ten synthetic datasets (see detailed
194 results in Supplementary Table 3), while Fig. 2d-l shows the Nelson-Aalen cumulative hazard functions (i.e., survival curves)
195 estimated from real training and test data, as well as from one representative synthetic dataset generated by each model,
196 selected to be closest to the mean of KM-D results for illustrative purposes. There are multiple notable findings here. First, the
197 cumulative hazard functions estimated from MeLD-generated synthetic data exhibit the closest agreement with that derived
198 from real data (Fig. 2a,b), yielding the largest *p*-value (mean [95% confidence interval]: 0.815 [0.521, 1.000]) and the smallest
199 KM-D (0.015 [0.005, 0.024]), as illustrated by the example in Fig. 2d. The other models produce remarkably smaller *p*-values
200 and larger KM-D. Second, current models display systematic biases by either 1) overestimating early death (e.g., HALO,
201 Fig. 2f) or 2) underestimating later death to varying degrees (e.g., SynTEG and TimeDiff, Fig. 2e,g). TimeAutoDiff, in contrast,
202 exhibits the greatest variability in its time-to-death estimates, indicating reduced stability (Fig. 2a,b). Third, all of the models
203 generate maximum follow-up time ranges longer than that observed in real data (Fig. 2c). However, MeLD produces the range
204 closest to that of real data. By contrast, SynTEG and TimeDiff yield follow-up ranges more than double the actual range
205 (36 years). Fourth, MeLD variants with alternative diffusion modules (MeLD-DDPM, MeLD-LSTM, and MeLD-DiT) all
206 demonstrate inferior performance than the standard MeLD, whereas MeLD-Transformer, despite its enhanced capability for
207 modeling temporal dependencies in VAE, does not lead to better time-to-death estimates. This highlights the advantages of the
208 MeLD architecture in faithfully reproducing time-to-death estimation.

209 We also evaluate the utility of synthetic data in reproducing the time-to-event analyses from ART initiation to the first
210 diagnosis event across 50 regularly collected clinical endpoints, encompassing conditions such as tuberculosis, diabetes, and
211 bone diseases. We conduct the same evaluation as in the time-to-death analysis, adding a Bonferroni correction to the log-rank
212 tests to account for multiple comparisons. We summarize results across the 50 clinical endpoints using 1) the false discovery rate
213 (FDR), calculated as the ratio of clinical endpoints where synthetic data exhibit significant differences, and 2) the distribution
214 of KM-D values.

215 MeLD and TimeDiff achieve the lowest FDR and KM-D values (Table 1). Moreover, all MeLD variants perform worse than
216 the standard MeLD in terms of FDR and KM-D values, with the exception of MeLD-Transformer, which yields comparable
217 KM-D values. These results support the same conclusion as the time-to-death estimations regarding the advantage of the
218 MeLD architecture. Further, the clinical endpoints most frequently misrepresented in time-to-diagnosis estimates vary in
219 their prevalence across models. MeLD and TimeDiff tend to misrepresent clinical endpoints with lower prevalence (<10%),
220 whereas other models are more likely to misrepresent those with higher prevalence (>10%), which are generally easier to model.
221 Taken together the time-to-death and time-to-diagnosis results, MeLD demonstrates the greatest data utility for time-to-event
222 estimation among all the models, whereas TimeDiff struggles to model longer-term dependencies like death.

223 Prediction

224 To examine the prediction utility of MeLD-generated synthetic data, we choose three disease prediction tasks relevant
225 to understanding disease progression for PWH, each with different prevalence and pathogenesis: the development of 1)
226 tuberculosis, 2) cancer, and 3) cardiovascular complications after six months of program enrollment. We use data observed
227 in the first six months as predictors to fit a simple one-layer GRU model. Predictors include demographics, weight, height,
228 CD4 cell count, HIV viral load, ART regimens, and clinical diagnoses. PWH diagnosed before six months are excluded from
229 the respective tasks. We evaluate predictive performance using AUROC on real test data, comparing training a classifier on
230 synthetic data (TSTR) to training it on real training data (TRTR).

231 MeLD ranks among the top-performing models across all three prediction tasks (Fig. 3, Supplementary Table 4), with
232 mean AUROC of 0.757 [0.741, 0.773], 0.626 [0.597, 0.655], and 0.615 [0.541, 0.689] for predicting tuberculosis, cancer,

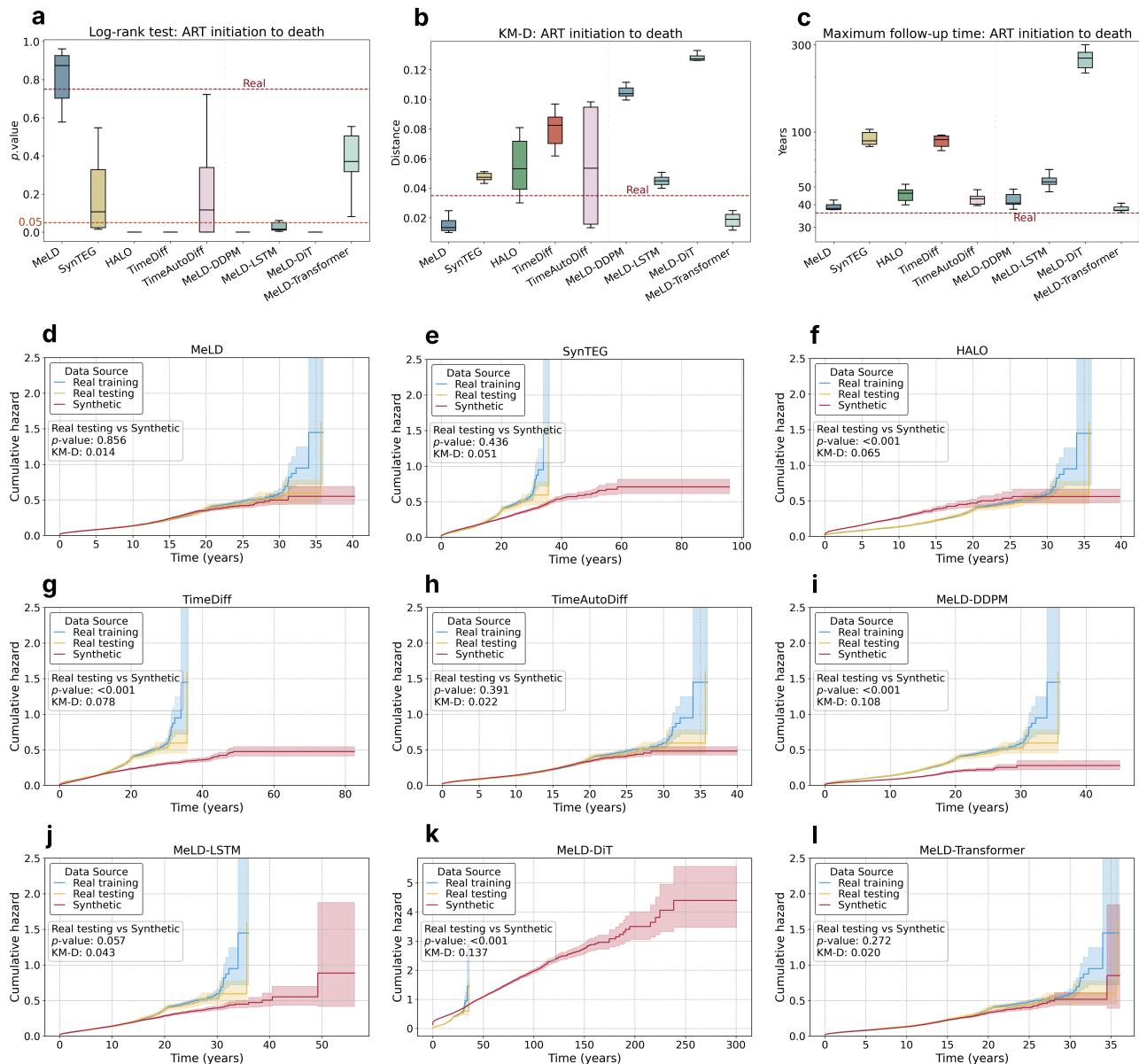


Figure 2. Comparison of performance in time-to-death estimation. Time from ART initiation to death is evaluated using: **a**, log-rank test p -values, **b**, Kaplan-Meier distance (KM-D), and **c**, maximum follow-up time, with real test data as the reference. Results based on real training data serve as the baseline, shown with red dashed lines. Boxplots are made with ten synthetically generated datasets. **d-l**, estimated Nelson-Aalen cumulative hazard functions of real training and test data, along with one synthetic dataset generated by each model, selected to be closest to the mean of KM-D values. KM-D between survival functions estimated from real test and synthetic data, as well as p -values from two-sided log-rank tests comparing estimated survival functions of real test and synthetic data are indicated.

Model	FDR from log-rank tests	KM-D distribution	Top-3 errors	Prevalence
Real training (vs. real test)	0	0.001 [0.000, 0.004]	-	-
MeLD	0.190 [0.144, 0.236]	0.003 [0.000, 0.014]	Diabetes Bone disease Dengue	2.09% 6.09% 0.83%
SynTEG	0.312 [0.259, 0.365]	0.006 [0.000, 0.035]	Dyslipidemia Diabetes Dengue	10.60% 2.09% 0.83%
HALO	0.212 [0.156, 0.268]	0.010 [0.000, 0.075]	Dyslipidemia Tuberculosis Cancer	10.60% 15.47% 3.34%
TimeDiff	0.100 [0.068, 0.132]	0.003 [0.000, 0.013]	Candidiasis pulm Pneumocystis Cytomegalovirus	1.12% 3.67% 0.80%
TimeAutoDiff	0.606 [0.536, 0.632]	0.007 [0.000, 0.036]	Dyslipidemia Tuberculosis Diabetes	10.60% 15.47% 2.09%
MeLD-DDPM	0.554 [0.487, 0.621]	0.011 [0.000, 0.080]	Dyslipidemia Tuberculosis Diabetes	10.60% 15.47% 2.09%
MeLD-LSTM	0.300 [0.248, 0.352]	0.006 [0.000, 0.050]	Tuberculosis Dyslipidemia Diabetes	15.47% 10.60% 2.09%
MeLD-DiT	0.936 [0.919, 0.953]	0.079 [0.000, 0.266]	Tuberculosis Cancer Toxoplasmosis	15.47% 3.34% 15.47%
MeLD-Transformer	0.290 [0.225, 0.355]	0.003 [0.000, 0.016]	Diabetes Dyslipidemia Dengue	2.09% 10.60% 0.83%

Table 1. Performance comparison in time-to-diagnosis estimation across 50 clinical endpoints. False discovery rate (FDR) from log-rank tests and KM-D values are derived using real test data as the reference. Results based on real training data serve as the baseline. 95% confidence intervals are reported over ten synthetically generated datasets. Best-performing results are highlighted in bold for comparisons between MeLD and existing models, as well as among MeLD variants. Top three clinical endpoints that are worst estimated are provided in descending order of their KM-D values, as well as their prevalence in real data.

233 and cardiovascular disease, respectively. Notably, for cancer prediction, models trained on MeLD-generated synthetic data
234 surpass those based on real training data. This might be attributed to the VAE component in MeLD, which removes noisy
235 relationships in cancer development when learning latent representations, thereby generating synthetic data with reduced noise.
236 Other models, by contrast, do not achieve consistently high rankings across tasks. For example, while TimeDiff exhibits top
237 and moderate performance for cardiovascular disease and tuberculosis prediction, respectively, it is near the bottom for cancer
238 prediction. HALO achieves the second best performance for cancer prediction, yet cancer is among the clinical endpoints that
239 are most misrepresented in its time-to-event analysis (Table 1). This discrepancy suggests that time-to-event analyses and
240 prediction tasks focus on complementary aspects of data utility and that reliable generative models should score well on both.
241

242 Among the MeLD variants, those using alternative diffusion modules exhibit lower prediction performance than the standard
243 MeLD across all tasks. In contrast, MeLD-Transformer performs well for all prediction tasks, achieving an AUROC comparable
244 to the TRTR scenario. Although MeLD-Transformer has a higher mean AUROC than MeLD, differences are minor, again
suggesting that substituting the temporal component in VAE with a transformer provides only marginal advantages.

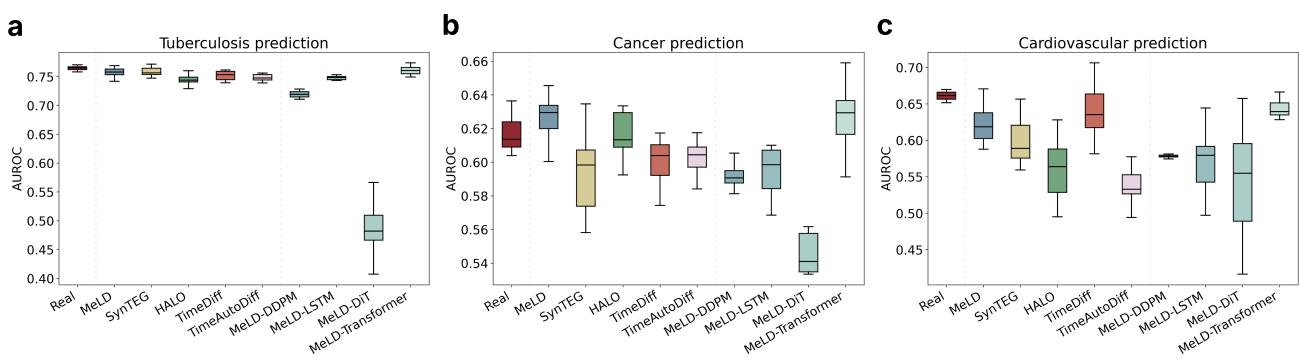


Figure 3. Comparison of performance in outcome prediction. Prediction performance on the real test data characterized by AUROC, is shown for **a**, tuberculosis, **b**, cancer, and **c**, cardiovascular diseases. Models are trained on data accumulated during the first six months post-enrollment to predict subsequent clinical endpoints. The scenario of training on real training data and testing on real test data serves as the baseline. Boxplots for synthetic data generation models are made with ten synthetically generated datasets, whereas those for training on real training data (TRTR) are based on ten random splits of the training and validation datasets.

245 Risk factor estimation

246 HIV researchers often estimate statistical associations between risk factors and clinical events to better understand disease
247 etiology, identify high-risk subgroups, and develop prevention and treatment strategies. Thus, a critical test of synthetic data
248 utility is whether it can preserve clinically meaningful associations. To examine this, we fit Cox proportional hazards models to
249 synthetic data to estimate the association between risk factors at ART initiation and mortality²⁷. We compare estimates to those
250 derived from real data to evaluate both the quality of the synthetic data and its potential applicability for clinical and public
251 health research. We include sex, age, CD4 cell count, and calendar year at ART initiation as covariates, with models stratified
252 by study site²⁸. For evaluation, we quantify three types of errors: 1) direction error: a significant estimate of a risk factor yields
253 a log-hazard ratio with an opposite sign in the synthetic data compared to the significant estimate from real data; 2) type I error:
254 a risk factor is significant in the synthetic data but not in the real data, and 3) type II error: a risk factor is significant in the real
255 data but not in the synthetic data. We then compare the log-hazard ratio values and corresponding confidence intervals of risk
256 factors estimated from real data and from MeLD-generated synthetic data.

257 Across all ten synthetic datasets and risk factors, MeLD produces the fewest errors for each type, as well as the lowest total
258 error (Fig. 4a). Specifically, MeLD makes only one type I error, which occurs for the age risk effect (Fig. 4b), and incurs no
259 type II or direction errors. This corresponds to an overall error rate of 2.5%. By contrast, all other models make errors across all
260 three types. For example, HALO-generated synthetic data produce 15 total errors (the second fewest), yet substantially higher
261 than MeLD. Other models exceed 37.5% total error rates, and all MeLD variants produce error rates >25.0%. While MeLD
262 produces the fewest errors, some of its estimates are biased compared to those from real data (Fig. 4b). For example, although
263 MeLD introduces no direction, type I, or type II errors for the calendar year log-hazard ratio, there is no confidence interval
264 overlap between any of MeLD's ten synthetic datasets and that from the real data. More details can be found in Supplementary
Table 5.

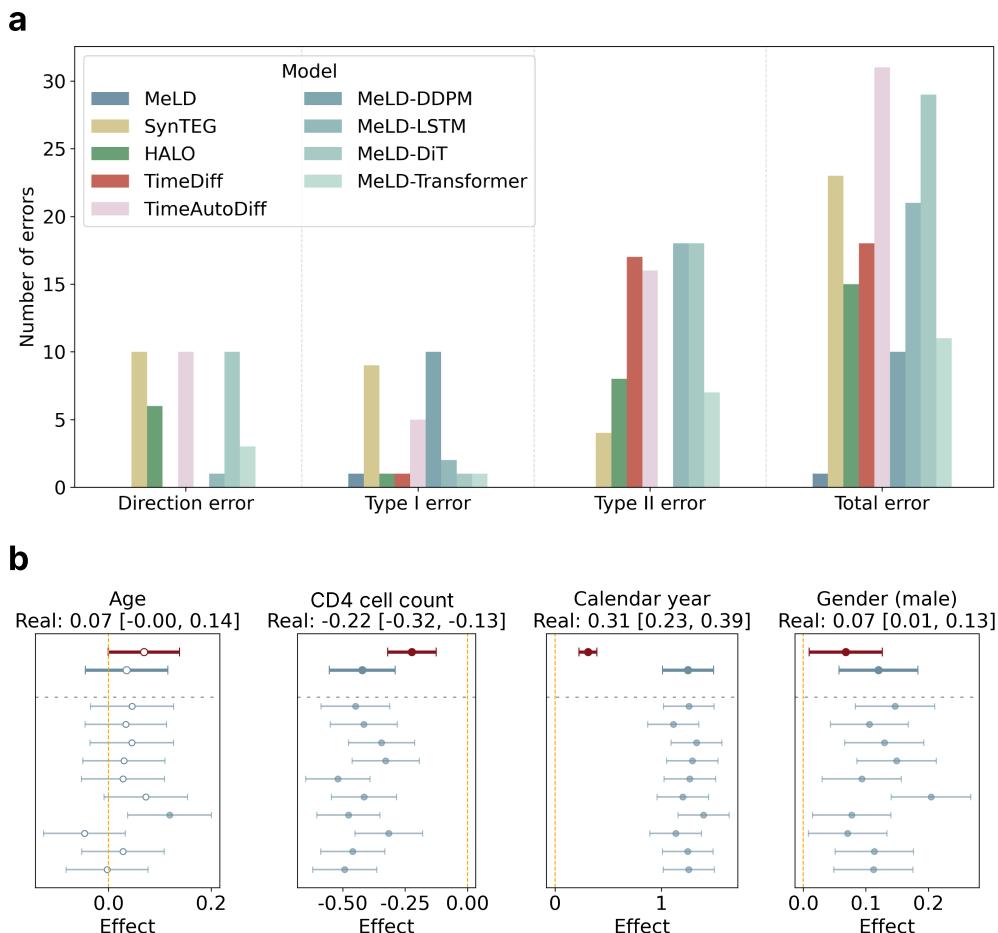


Figure 4. Error analysis for risk factor estimation. **a**, Aggregated errors from Cox proportional hazard models evaluated on ten synthetic datasets across four risk factors. A direction error occurs when a significant estimate of a risk factor yields a log-hazard ratio with an opposite sign in the synthetic data compared to the real data; a type I error occurs when a risk factor is identified as significant in the synthetic data but not in the real data; a type II error occurs when a risk factor that is significant in the real data is missed in the synthetic data. **b**, Forest plots of log-hazard ratio risk factor estimates from MeLD's ten synthetic datasets and their aggregated estimates using Rubin's Rule (bold blue), alongside estimates from real data (bold red). Non-significant estimates are indicated using hollow-centered circles.

266 Data Fidelity

267 Data fidelity focuses on evaluating the statistical properties of synthetic data that are independent of specific applications and
268 determining how well they mirror those of real data. High-fidelity synthetic longitudinal cohort data should demonstrate close
269 resemblance in terms of variable-level distributions, correlations, latent clustering consistency, individual-level medical concept
270 abundance, and overall missingness patterns.

271 *Variable-level distribution*

272 For continuous variables, we assess: 1) total number of visits, 2) inter-visit time gaps, 3) weight, 4) height, 5) enrollment
273 age, 6) CD4 cell count, and 7) HIV viral load. We use Wasserstein distance (WSD) to measure the differences between real
274 and synthetic data, which is defined as the minimum amount of probability mass that must be transported to transform one
275 distribution into the other.

276 There are several notable findings. First, MeLD-generated synthetic data yield the lowest WSD for five of the seven
277 continuous variables, while ranking second for the other two (age and CD4 cell count) (Fig. 5a, Supplementary Table 6).
278 Second, the distribution of the total number of visits varies markedly across models, as shown by a representative synthetic
279 dataset for each model in Fig. 5c-g. MeLD, HALO, and SynTEG all use the EOS token to indicate the final visit; however,
280 while MeLD and HALO produce visit number distributions closely resembling those in real data, SynTEG generates data
281 with substantially fewer visits. TimeDiff and TimeAutoDiff do not employ the EOS token but create opposite effects: the
282 former oversamples individuals with a high number of visits, whereas the latter undersamples them. Third, while all models
283 successfully capture the modes of CD4 cell count and HIV viral load, they struggle to represent the low-density regions
284 observed in real data (Supplementary Fig. 1). Fourth, among MeLD variants, MeLD-Transformer demonstrates the closest
285 fidelity to MeLD across continuous variables (Supplementary Table 6), whereas the other variants perform worse on most
286 variables.

287 For categorical variables, such as clinical diagnoses and medications, we follow the approach of Theodorou *et al.*²² and
288 examine aspects at both the person- and visit-level: 1) frequencies of medical concepts (referred to as concept probability), 2)
289 frequencies of medical concept bigrams (referred to as bigram probability), focusing on the co-occurrence of medical concepts
290 within the same visit, and 3) frequencies of sequential medical concept bigrams (referred to as sequential bigram probability),
291 focusing on the occurrence of medical concepts in consecutive visits. We quantify the deviation of synthetic data from real
292 training data with respect to each of these measures using the mean absolute error (MAE).

293 MeLD consistently achieves the lowest normalized MAE across all measures (Fig. 5b, Supplementary Fig. 2, Supplementary
294 Table 7), highlighting its ability to capture not only the marginal distributions of categorical variables and the co-occurrence of
295 medical concepts within the same visit, but also their sequential occurrence across visits.

296 *Correlation*

297 Variable correlation characterizes how well synthetic data preserve the inter-variable relationships observed in the real data.
298 We examine two types of correlations: 1) between-individual correlation, which relates individual-level means (e.g., each
299 individual's mean CD4 cell count value or treatment frequency) across PWH to reveal whether individuals with higher values
300 in one variable also tend to be higher on the other, and 2) within-individual correlation, which relates visit-level deviations from
301 each individual's own mean (e.g., how two variables co-fluctuate around that individual's baseline). We calculate Spearman
302 correlation for both types across all variable pairs and report the sum of differences between synthetic and real data using
303 Frobenius norm.

304 Similar model rankings are observed in between- and within-individual correlations (Fig. 6a,b, Supplementary Fig. 3),
305 with MeLD achieving the closest correlations to real data. Although MeLD-Transformer achieves the lowest Frobenius norm
306 distance among MeLD variants, it is outperformed by standard MeLD.

307 *Latent clustering consistency*

308 Latent clustering consistency characterizes the ability of synthetic data generation models to capture the joint distribution
309 of all variables in real data. The procedure is conducted in the underlying latent space by 1) merging records from real and
310 synthetic datasets, 2) applying principal component analysis and retaining components explaining 80% of the system variance,
311 3) conducting K-means clustering to identify clusters, and 4) assessing cluster-level compositions of real versus synthetic
312 records using normalized mutual information (NMI), which measures the mutual information between cluster assignments and
313 source labels (real versus synthetic), with the values of 0 and 1 corresponding to the best and worst fidelity of synthetic data,
314 respectively. Synthetic data of high fidelity should produce cluster compositions that are inseparable from real data in the latent
315 space.

316 The experiments show that MeLD generates synthetic data that are nearly indistinguishable from real data in the latent
317 space (Fig. 6c, Supplementary Table 8), achieving a markedly low average NMI of 0.0003. TimeDiff and SynTEG, by contrast,
318 exhibit the highest average NMI values of 0.0377 and 0.1117, respectively. These discrepancies are in alignment with the

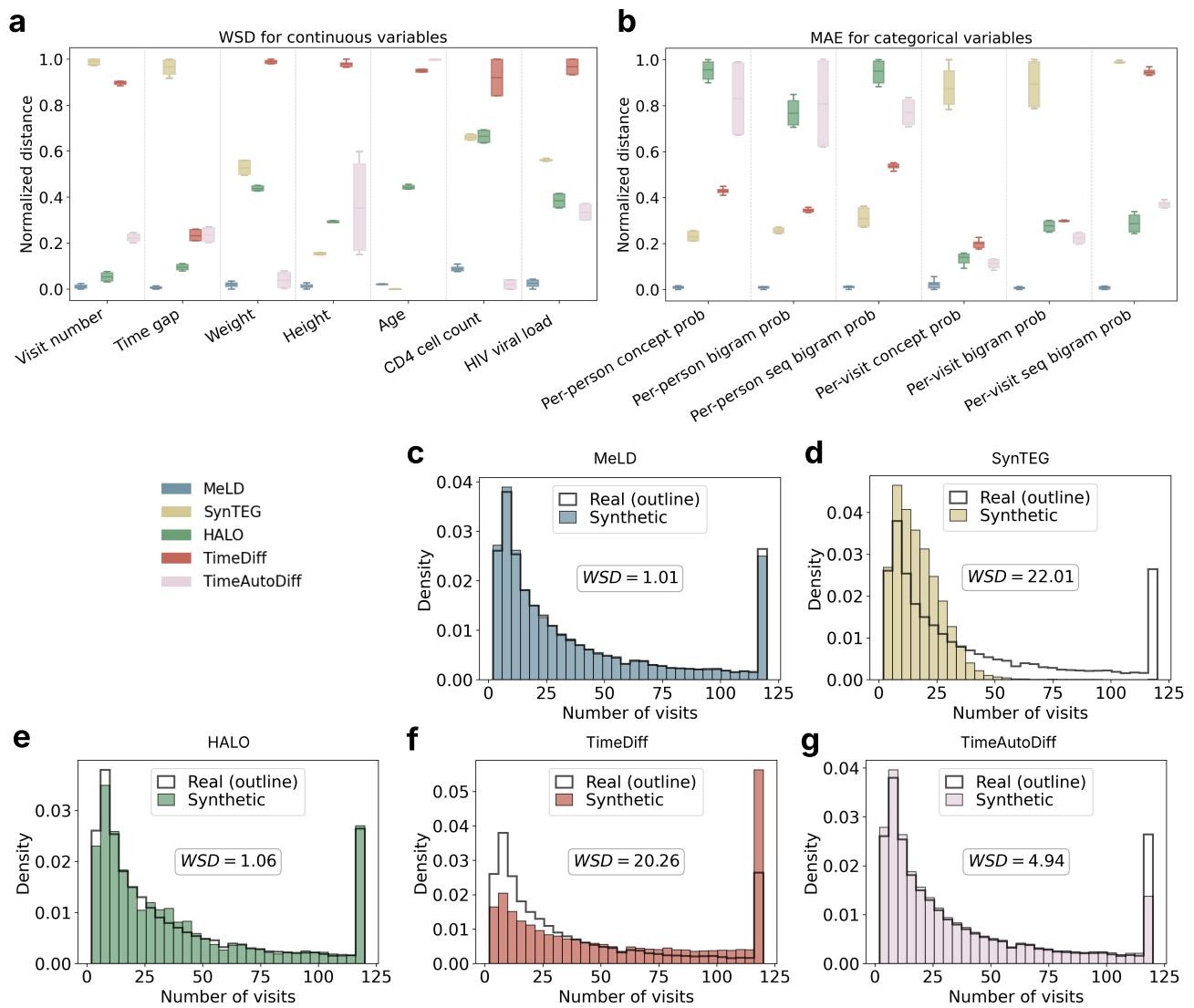


Figure 5. Fidelity comparison in terms of variable-level distributions. **a**, Normalized Wasserstein distance (WSD) of continuous variables, with raw values linearly mapped to the [0,1] range for each variable. **b**, Normalized mean absolute error (MAE) across categorical variables, measured using per-person and per-visit probabilities of single, bigram, and sequential bigram concepts, with raw MAE values linearly mapped to the [0,1] range. **c-g**, Probability distributions of visit numbers of real data, along with one synthetic dataset generated by each model, selected to be closest to the mean of WSD values.

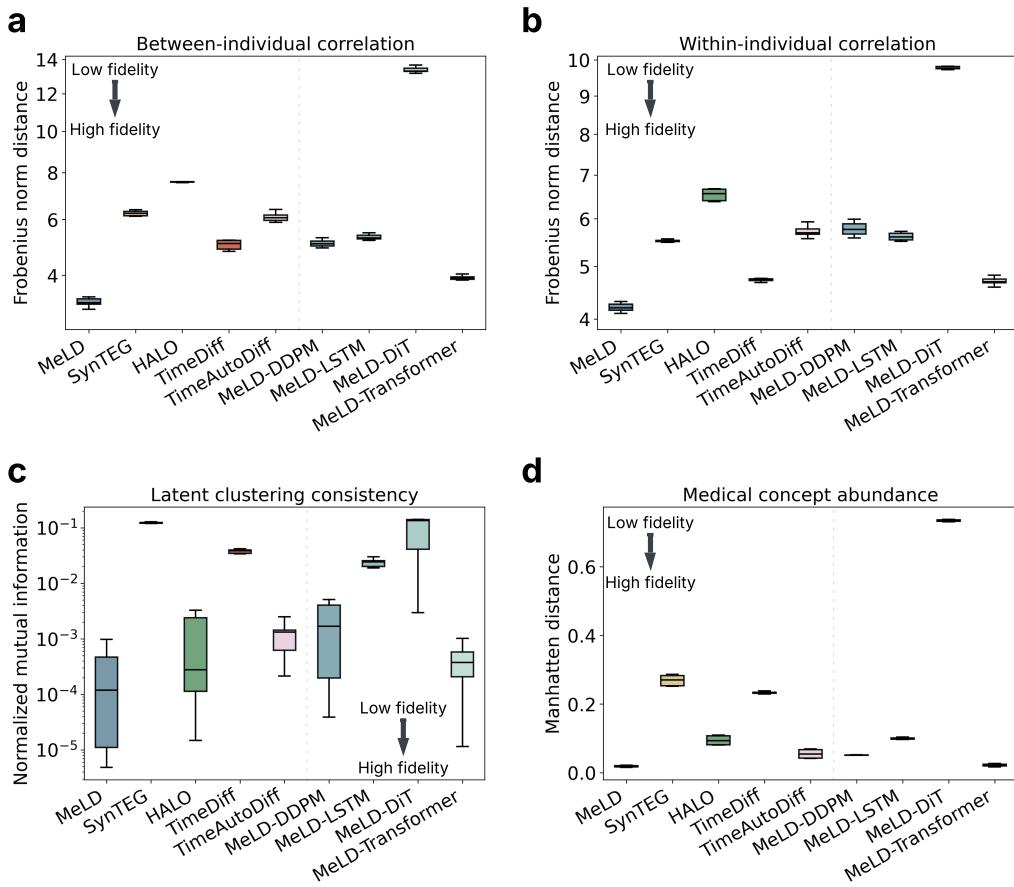


Figure 6. Data fidelity assessment in terms of **a**, between-individual correlation, **b**, within-individual correlation, **c**, latent clustering consistency, and **d**, medical concept abundance. Boxplots are made with ten synthetically generated datasets.

319 fidelity gap observed in other metrics that focus on the original space. Of all MeLD variants, only MeLD-Transformer matches
 320 the standard MeLD model's performance, whereas the rest show inferior NMI.

321 **Medical concept abundance**

322 We also investigate the degree to which synthetic data generators capture the quantity of individual-level information in real
 323 data with medical concept abundance (MCA)⁴. MCA, originally designed for cross-sectional data, uses the total number of
 324 clinical events in each individual as a proxy for severity of illness or health status. We extend MCA to the longitudinal setting by
 325 aggregating visit-level MCA values and then normalizing the aggregated values with the total number of visits. The difference
 326 in the MCA distribution between real and synthetic data is then calculated using the Manhattan distance⁴.

327 MeLD shows the smallest MCA difference between real and synthetic data among all models, suggesting that it best
 328 preserves the overall health status distribution in real data (Fig. 6d). Moreover, the MeLD variants with different diffusion
 329 components underperform relative to MeLD, whereas MeLD-Transformer achieves a similar MCA difference.

330 **Missingness pattern**

331 Missing data are ubiquitous in observational data from healthcare records. Generating synthetic longitudinal clinical cohort data
 332 that replicate the missingness patterns observed in real data is essential to ensure realistic data quality and maintain the validity
 333 of downstream applications. Since MeLD is the only model that explicitly accounts for missingness during model training and
 334 data generation, we compare the missingness patterns between MeLD-generated synthetic data and real data prior to imputation
 335 across all continuous variables with missingness: i.e., CD4 cell count, HIV viral load, weight, and height. Missingness for each
 336 variable is characterized by two measures: 1) the overall variable-level proportion of missingness across the entire cohort (a
 337 scalar) and 2) the individual-level proportion of missingness (a distribution). It is notable that MeLD closely reproduces the
 338 proportions of missingness observed in real data, with both variable- and individual-level proportions of missingness falling

339 within similar ranges across all variables (Table 2).

Variable	Variable-level proportion of missingness		Mean individual-level proportion of missingness	
	Real	Synthetic	Real	Synthetic
CD4 cell count	0.826	0.818 [0.816, 0.819]	0.808	0.808 [0.806, 0.809]
HIV viral loads	0.944	0.945 [0.944, 0.946]	0.923	0.926 [0.925, 0.927]
Weight	0.695	0.685 [0.683, 0.687]	0.734	0.736 [0.734, 0.738]
Height	0.947	0.949 [0.948, 0.949]	0.931	0.936 [0.935, 0.937]

Table 2. Comparison of proportions of missingness between real and MeLD-generated synthetic data. Variable-level and mean individual-level proportions of missingness are reported for both real and synthetic datasets. For each metric, 95% confidence intervals are estimated over ten independently generated synthetic datasets by MeLD. Note that the definition of missingness used here differs from that used in epidemiological analyses: for any given measurement, all visits lacking an observed value are considered missing, regardless of whether the value was unmeasured, intentionally omitted, or below the detection limit.

340 **Privacy**

341 To evaluate the privacy risks posed by sharing synthetically generated data, we investigate three well-studied measures: attribute
342 inference^{29,30}, membership inference^{29,30}, and nearest neighbor adversarial accuracy (NNAA)³¹. For both attribute inference
343 and membership inference, we make a reasonable assumption that the adversary has access to synthetic data but not to the
344 underlying data generators. Real training data are used to simulate a reference scenario where this dataset is accessible to the
345 adversary.

346 • Attribute inference occurs when an adversary uses synthetic data to infer unknown sensitive attributes from partial
347 knowledge of real data. It is assumed that the adversary knows the demographic information and the 100 most common
348 medical concepts (representing an upper bound on adversarial capability to stress-test the system) of 5,000 randomly
349 sampled real training records. Using a K-nearest neighbor (KNN) algorithm, the most similar synthetic record among
350 5,000 sampled is identified to infer the value of the remaining variables. F1 score is used to quantify attack performance.

351 • Membership inference risk measures the extent to which an adversary can infer whether an entire real record they have
352 access to was part of the real training data used to train the synthetic data generator. We assume that the adversary has
353 access to a set of real records comprising 5,000 randomly sampled real training records and 5,000 randomly sampled real
354 test records, without knowledge of their affiliation. The adversary infers that a real record was a member in the training
355 data based on its closest distance to synthetic records, using median distance as cutoff. The proportion correctly classified
356 is computed. A sensitivity analysis is also performed on a wide range of distance cutoffs.

357 • NNAA risk measures the degree of overfitting of a synthetic data generator to the real training data, using a held-out real
358 dataset (e.g., real test set) as a reference. When a synthetic data generator inappropriately memorizes real training data
359 rather than generating novel samples, the generated synthetic records tend to be systematically closer to real training
360 data than to the held-out real test data. To measure NNAA risk, we randomly sample 5,000 records each from the real
361 training, real test, and synthetic datasets, and compare the aggregated minimum distance of each synthetic record to their
362 nearest neighbor in the real training and test sets, and vice-versa. A positive NNAA value indicates that synthetic data are
363 closer to the training data and vice-versa. We use a threshold of 0.03 to determine model overfitting, as suggested by Yale
364 et al.³¹.

365 Fig. 7 depicts the three privacy risk metrics for the synthetic data generated by MeLD and the baseline models, and reveals
366 several notable findings. First, attribute inference risks, characterized by F1 scores, range from 0.020 to 0.050 across all models,
367 suggesting that attribute inference attacks in general are ineffective for both MeLD and other synthetic data generators. MeLD
368 ranks in the middle, and its variants exhibit comparable levels of risk (Supplementary Table 9). Second, except for HALO,
369 membership inference risks are nearly the same for all models, achieving an accuracy around 0.510, which is similar to random
370 guessing. A sensitivity analysis across a wide range of distance cutoffs produces consistent observations (Supplementary
371 Fig. 4). Third, MeLD attains an average NNAA risk of -0.0008, substantially below 0.03 threshold, suggesting minimal model
372 overfitting. In contrast, such risk is elevated for TimeDiff (0.031 [0.012, 0.050]), a level that can cause privacy leakage. In
373 summary, MeLD and its variants maintain strong privacy protection, which implies that improved utility and fidelity are not
374 achieved at the expense of privacy.

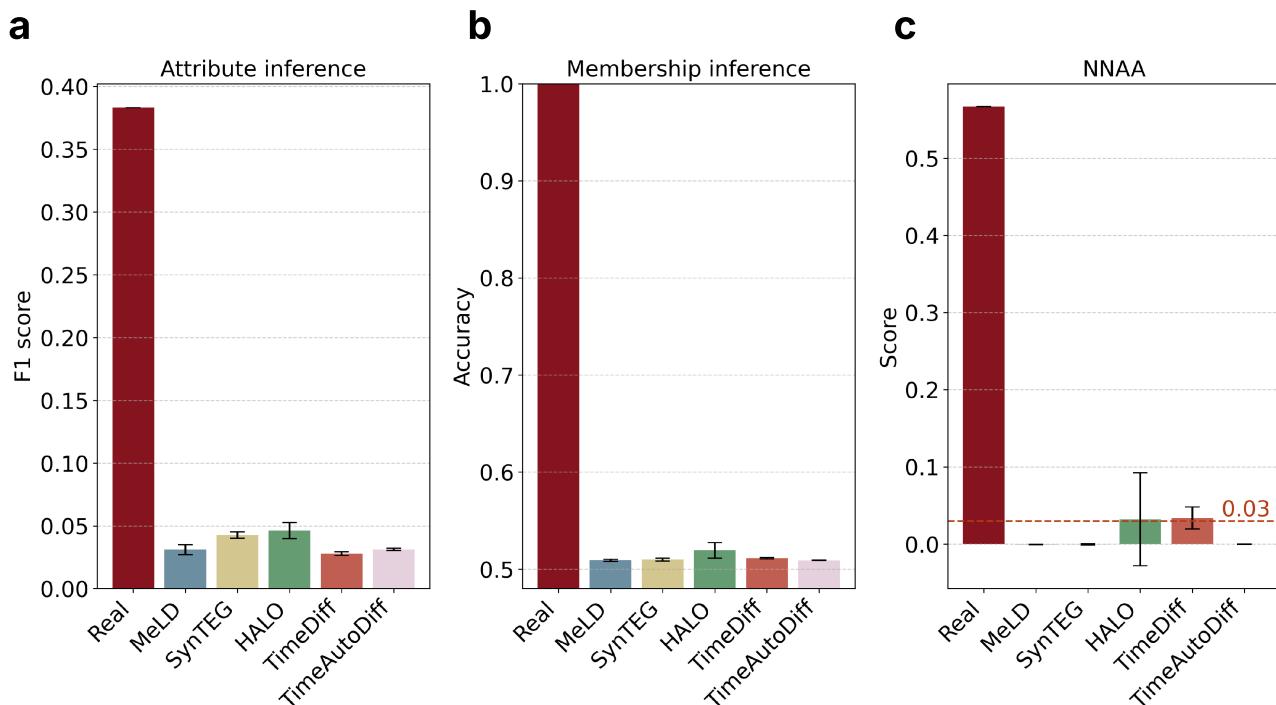


Figure 7. Privacy risk evaluation. **a**, F1 score of attribute inference attack. **b**, accuracy of membership inference attack. **c**, NNAA risk. The risks associated with real data are shown in the leftmost red bars. NNAA risk less than 0.03 is deemed acceptable. 95% confidence intervals are estimated over ten synthetically generated datasets. NNAA=nearest neighbor adversarial accuracy.

375 Discussion

376 Generating long synthetic data sequences has been a challenge across a variety of domains, particularly in time-series modeling
377 that contains a large number of mixed-type variables³². MeLD addresses this issue through a latent diffusion-based framework
378 integrated with a transformer backbone, which enables the generation of long-term health trajectories with realistic longitudinal
379 dependencies. Our empirical investigation demonstrates that MeLD substantially outperforms state-of-the-art methods designed
380 for longitudinal EHR data generation across evaluation dimensions (Fig. 1e). Notably, MeLD achieved the best fidelity in
381 both continuous and categorical variables, highlighting its flexibility in handling mixed-type data. MeLD also exhibited
382 the strongest consistency in capturing both within- and between-individual correlations. Moreover, the close alignment in
383 latent-space structure and medical concept abundance reaffirms that MeLD effectively generates synthetic data following
384 the joint distribution of the real data. Importantly, MeLD is also designed to natively handle missingness in cohort data, a
385 fundamental characteristic of real-world observational data that most previous studies have overlooked. We attribute these
386 encouraging results to the versatility of the VAE architecture and the exceptional generative capabilities of the diffusion
387 transformer. Specifically, our VAE's encoder design embeds complex data patterns into a unified latent representation, allowing
388 the diffusion module to learn and generate data without directly dealing with the complexity of the original feature space.
389 Meanwhile, the transformer-based diffusion mechanism allows MeLD to effectively capture global population structures and
390 generates detailed temporal and cross-sectional patterns, resulting in synthetic cohorts that closely mirror real-world individual
391 variability.

392 Our focus on assessing the utility of synthetic longitudinal cohort data through time-to-event analyses and risk-factor
393 estimation represents a largely unexplored yet critical dimension of synthetic health data research. Unlike most prior studies
394 that produce general-purpose synthetic data and narrowly assess data utility for predictive modeling or data augmentation, our
395 research explicitly examines synthetic data capability to support inferential tasks that are central to clinical and epidemiological
396 research. This focus closely aligns the broader vision of leveraging synthetic data to enable scientific hypothesis generation.
397 While one cannot enumerate all potential hypotheses for utility evaluation, evaluating their performance through representative
398 inferential or replication-oriented tasks provides a practical and rigorous means to estimate their real-world research value.

399 Prior evidence suggests that synthetic data tend to produce unacceptably high error rates, particularly false-positive findings
400 (type I errors)³³. In contrast, our evaluation demonstrates that MeLD commits only a single error across 40 tested scenarios,
401 generally preserving the underlying statistical relationships. This type of evaluation, as well as the encouraging results, establish
402 an empirical foundation for considering synthetic longitudinal data as a credible bridge toward exploratory analysis and
403 hypothesis-driven biomedical research.

404 Throughout the experimental results, we observed that architectural choices play a critical role in preserving long-range
405 temporal coherence. Even when using real clinical visit sequences containing up to 120 visits and spanning more than three
406 decades, MeLD demonstrated advantages over state-of-the-art designs in capturing long-range dependencies. Further notable,
407 replacing a GRU with a transformer in the VAE component of MeLD did not produce a clear performance advantage. This
408 observation likely reflects the functional division within the latent diffusion design, where VAE's RNN is responsible for
409 learning temporal dependency between visits and aligning them closely in latent space³⁴, whereas the transformer in the
410 diffusion component captures higher-order temporal structure and drives generative dynamics. As a result, a lightweight GRU
411 fulfills the VAE's role in this design.

412 While MeLD demonstrates the strongest overall performance, some metrics still favor specific existing models. For example,
413 TimeDiff, an LSTM-based diffusion model, achieves the lowest FDR in time-to-diagnosis analyses. This advantage likely
414 reflects the short time-to-disease durations in the real cohort of PWH. In such conditions, recurrent architectures like LSTM may
415 better capture short-term temporal dependencies. However, its advantage diminishes for outcomes requiring modeling extended
416 temporal horizons, such as maximum follow-up time and time-to-death, where MeLD demonstrates superior robustness.
417 Similarly, HALO and SynTEG outperform MeLD in capturing the tails of continuous variable distributions (Supplementary
418 Fig. 1). This difference arises because both models apply post-hoc sampling from the discretized empirical distributions for
419 reconstruction, whereas MeLD reconstructs data directly from a compressed latent representation. Consequently, MeLD
420 follows the VAE's tendency to emphasize high-probability regions of the data space, leading to slightly reduced tail coverage.
421 Nonetheless, this mechanism allows MeLD to achieve higher fidelity in overall distribution and inter-variable correlations.

422 The tradeoff between data utility and privacy in machine learning-based synthetic health data generation has been reported
423 in multiple prior studies, where higher utility is generally linked to lower privacy protection (or higher risks), and vice versa^{3,4}.
424 In these works, “utility” is typically defined in terms of fidelity to real data and performance on downstream tasks. Most of
425 these observations are derived from synthetic snapshot or cross-sectional health tabular data. However, we do not observe such
426 a phenomenon in the scenario of synthetic longitudinal clinical cohort generation. Specifically, MeLD, the generator achieving
427 the highest performance in nearly all utility and fidelity metrics, also exhibits low privacy risks, compared to state-of-the-art
428 models. This observation implies that the conventional utility-privacy Pareto frontier observed in prior research may not
429 apply to all modeling scenarios. Rather, it reflects the limited representational capability of previous models to learn complex
430 longitudinal structures without memorizing individual data patterns. MeLD's architectural design may allow the model to
431 capture high-level regularities from real data while reducing the likelihood of reproducing real data. As a result, we believe
432 the existing frontier between utility and privacy is not necessarily optimal in synthetic longitudinal cohort generation, and
433 substantial opportunities remain for innovation in model design to enhance data utility and fidelity without sacrificing privacy.

434 We are releasing MeLD as an open-source tool, so that it can enable HIV researchers, and epidemiologists more broadly,
435 conducting cohort studies to generate and share synthetic datasets to facilitate research replication and transparency. We
436 believe MeLD bridges the long-standing divide between data protection and utility, and paves the way for a more inclusive,
437 collaborative, and reproducible era of global HIV and epidemiological research. Beyond a methodological advance, we are
438 releasing the synthetic cohort of PWH generated by MeLD, which is composed of over 49,000 simulated PWH. This dataset
439 represents the first high-quality synthetic longitudinal cohort of PWH that mirrors the structural and temporal complexity of data
440 typically seen in large international HIV consortia. This will enable researchers with diverse expertise backgrounds, particularly
441 those without access to proprietary cohort data, to actively engage in hypothesis generation, methodological innovation, and
442 model benchmarking, thereby accelerating the advancement of HIV research and treatment. This dataset can also be used in
443 education and training in HIV medicine by allowing trainees to interact with and explore real-world-like datasets. We note that
444 Kuo *et al.*³⁵ also released a synthetic cohort of PWH, but that their dataset contains substantially fewer variables and limited
445 clinical depth (15 variables) compared to MeLD.

446 While our results suggest that MeLD is a major step forward in longitudinal synthetic data generation, there are opportunities
447 for future improvement. First, the evaluation of MeLD is conducted using a single longitudinal dataset, which may limit the
448 generalizability of our findings. Broader evaluations of MeLD across additional chronic diseases and data settings will be
449 pursued in future studies. Nevertheless, the CCASAnet cohort, one of the largest and most diverse international HIV datasets,
450 offers extensive population heterogeneity and a harmonized data structure, which enhance the external relevance of our results
451 to other HIV consortia. Second, our evaluation includes four state-of-the-art models but does not cover all existing methods for
452 longitudinal data generation, such as TarDiff³⁶, FourierFlow³⁷, DiffusionTS³⁸, TimeGAN³⁹, and TimeVAE⁴⁰. TarDiff is tailored
453 for generating synthetic longitudinal health data that are particularly helpful in improving fairness in specific downstream

454 prediction tasks, while FourierFlow and DiffusionTS target univariate time-series generation, making them less suitable for our
455 objective of modeling multivariate clinical trajectories. TimeGAN and TimeVAE, although well-known, are not considered
456 state-of-the-art and have been shown to perform less effectively than the baseline models we select⁸. Our selected baseline
457 models encompass the primary generative AI paradigms for general-purpose synthetic longitudinal data generation, providing a
458 representative foundation for our evaluation. Lastly, synthetic data might introduce bias and fairness issues that affect data
459 quality across subgroups. This study does not perform group-specific evaluations and MeLD is trained without conditional
460 guidance, which could affect subgroup fidelity. Addressing these issues represents an important avenue for future research.

461 Methods

462 Data

463 This study uses the PWH cohort data from the Caribbean, Central and South America Network for HIV Epidemiology
464 (CCASAnet)⁴¹, comprising information collected from HIV clinical sites in seven countries: Centro Medico Huesped, Buenos
465 Aires, Argentina (Argentina-CMH); Instituto de Pesquisa Clinica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro,
466 Brazil (Brazil-FC); Fundacion Arriaran, Santiago, Chile (Chile-FA); Les Centres GHESKIO, Port-au-Prince, Haiti (Haiti-
467 GHESKIO); Instituto Hondureño de Seguridad Social and Hospital Escuela, Tegucigalpa, Honduras (Honduras-IHSS/HE);
468 Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (Mexico-INCIMNSZ); and
469 Instituto de Medicina Tropical Alexander von Humboldt, Lima, Perú (Peru-IMTAvH). Clinical data were collected at each
470 site, de-identified, and sent to the CCASAnet Data Coordinating Center at Vanderbilt University (Nashville, TN, USA) for
471 harmonization and processing. This study does not include data from Peru because its approval period differs from that of the
472 other sites. Institutional ethics review boards from all other sites and Vanderbilt University reviewed and approved the project.
473 All PWH of at least 18 years old at the time point of program enrollment, who have at least 2 visits are included in this study.
474 Descriptive statistics of the dataset are shown in Supplementary Table 1, and the variable list can be found in Supplementary
475 Table 2.

476 Given the study population $\{\mathbf{x}_i\}_{i=1}^N$, we adopt the standard notation for longitudinal EHR data, where the record of individual
477 i with t_i historical visits is denoted as $\mathbf{x}_i = [\mathbf{x}_{i,1}, \mathbf{x}_{i,2}, \dots, \mathbf{x}_{i,t_i}]$. Each visit shares the same set of J variables, and the trajectory
478 of variable j across all visits is represented as $\mathbf{x}_{i\cdot,j}$. It is important to note that the original clinical cohort data are typically
479 1) organized in a set of relational database tables and linked through unique identifiers, 2) longitudinal with variable-length
480 follow-up: each individual's record $\mathbf{x}_{i,1:t_i}$ ($i \in \{1, 2, \dots, N\}$) is a sequence of visits of length $t_i \leq T$, where T represents the
481 maximum number of visits across the cohort, and 3) of mixed-type: each visit $\mathbf{x}_{i,t} = [\mathbf{x}_{i,t}^C, \mathbf{x}_{i,t}^D]$ consists of s continuous variables
482 $\mathbf{x}_{i,t}^C = [x_{i,t,1}, \dots, x_{i,t,s}] \in \mathbb{R}^s$ and k binary variables $\mathbf{x}_{i,t}^D = [x_{i,t,s+1}, \dots, x_{i,t,s+k}] \in \{0, 1\}^k$, which can be derived from categorical or
483 discrete variables.

484 To preprocess the original CCASAnet data, we integrate visit information of medical events from distinct tables, as well
485 as corresponding timestamps, into unified clinical entries. More concretely, laboratory measurement results (e.g., CD4 cell
486 count and HIV viral load) and medical concepts (e.g., clinical diagnoses and treatment regimens) are integrated into visit-level
487 representations, ensuring that all relevant information for each visit is consolidated into a single clinical entry. Inter-visit time
488 gaps are added as a continuous variable to each visit. All continuous variables are normalized to $[0, 1]$ in a linear manner,
489 whereas categorical variables are encoded as one-hot representations. Inspired by HALO²², demographic information (i.e.,
490 age, sex, and site) is indicated in “visit 0”. These processing steps yield a complete clinical visit sequence $\mathbf{x}_{i,1:t_i}$, where each
491 entry contains a snapshot of the individual's health status corresponding to a specific clinical visit. To manage computational
492 efficiency, we limit each individual's record to a maximum of $T = 120$ visits, which corresponds to the 90th percentile of visit
493 counts across the cohort. The resulting preprocessed dataset contains 135 variables and an average of 45 visits per person,
494 spanning over three decades.

495 To enable batch processing of variable visit lengths, we use $\mathcal{E}^{(N,T)} = \{\mathbf{x}_{i,1:T}^{eos}\}_{i=1}^N$ to denote the end-of-sequence (EOS)
496 tokens, where $x_{i,t}^{eos} = 1$ if visit t is the last visit (i.e., $t = t_i$), and $x_{i,t}^{eos} = 0$ otherwise. Moreover, we introduce $\mathcal{P}^{(N,T)} = \{\mathbf{x}_{i,1:T}^{pad}\}_{i=1}^N$
497 to denote the masking tokens used to mark the padding positions $x_{i,t}^{pad} = I(\sum_{q=1}^t x_{i,q}^{eos} - x_{i,t}^{eos} > 0)$. This enables implementing
498 zero-padding to construct a uniform-length data matrix $\mathcal{X}^{(N,T,s+k)} = \{[\mathbf{x}_{i,1:t_i}, \mathbf{0}_{t_i+1:T}]\}_{i=1}^N$. In addition, the timestamps of all
499 individuals' records are represented as time tokens $\mathcal{T}^{(N,T)}$.

500 To explicitly handle missing data in relevant continuous variables, whether due to uncollected values during clinical visits
501 or laboratory results falling below detection limits, we use $\mathcal{M}^{(N,T,s)} = \{[\mathbf{x}_{i,1:t_i}^M, \mathbf{0}_{t_i+1:T}]\}_{i=1}^N$ as the missingness indicators to
502 mark missing entries, where $x_{i,t,j}^M = 1$ indicates a missing value, and $x_{i,t,j}^M = 0$ otherwise. MeLD leverages these tokens within
503 the input data to capture missingness patterns while masking out missing values so that model training focuses on the observed
504 values. In the post-processing stage, we use the learned missingness indicators to determine the positions of missing values. For
505 a fair comparison with models that do not natively handle missing values, missing values are imputed with Multiple Imputation

506 by Chained Equations (MICE)²⁵ before training.

507 Model architecture

508 As illustrated in Fig. 1, MeLD contains two major components: 1) a variational auto-encoder (VAE) that learns a mapping
509 between the original sparse, mixed-type data space and a dense, continuous latent space, and 2) a transformer-based diffusion
510 model to generate synthetic longitudinal visits in the latent space.

511 (1) **VAE:** Variables of each data type stream are first embedded through the corresponding embedding layer. An MLP layer
512 then takes the concatenation of embeddings from all variable type streams and fuses them into a unified embedding.
513 The fused embedding, sized (N, T, H) , is reshaped into (NT, H, B) using a 1D convolution layer with B channels. This
514 flattened representation is then passed into a transformer encoder to learn the dependencies among variables, with
515 the output being reshaped back to (N, T, H) via another 1D convolution layer. Next, the output, together with MLP-
516 embedded real timestamps and position-encoded visit indices, are passed into two RNN modules in parallel to learn
517 temporal dependency, yielding μ_z and σ_z^2 as the mean and variance of the approximate posterior distribution over the
518 latent variables. The decoder takes the synthetically generated visit sequence in the latent space, sized (N, T, L) , as
519 input, transforms it using an MLP, and finally applies type-specific linear projections to map them back to the original
520 spaces. This architecture follows the TimeAutoDiff VAE in design, but largely enhances its capability and flexibility by
521 incorporating the EOS signals and missingness so that MeLD can more accurately replicate follow-up complexity and
522 missingness patterns in longitudinal clinical cohorts.

523 (2) **Transformer-based diffusion:** We adapt DiT¹⁹, a transformer-based diffusion model designed for image generation,
524 to the task of clinical visit sequence generation. Specifically, data sampled from the latent space learned by the VAE
525 encoder are used as input with dimension (N, T, L) , and are iteratively corrupted with Gaussian noises during the forward
526 process of diffusion. Corrupted latent visit sequences are then leveraged to iteratively remove the added noises and finally
527 recover the underlying latent visit sequences. In particular, at each reverse step, input data are first transformed via a 1D
528 convolution layer for patchification and passed to a stack of DiT modules for dependency modeling and noise prediction.
529 In our design, we treat each visit as an individual patch for convenience. Within the DiT module, the patched sequences
530 passes through normalization, attention, and point-wise feedforward layers. In addition, the timesteps of the diffusion
531 process serve as a conditional input for DiT, which are first embedded with an MLP layer and then applied to scaling and
532 shifting transformation before and after the attention and the feed-forward layers in DiT.

533 Beyond the aforementioned overall design, MeLD introduces multiple architectural innovations compared to baseline
534 models. First, unlike the TimeAutoDiff VAE, which creates a separate embedding for each variable, an approach that scales
535 poorly with a large number of variables, we employ a more efficient strategy that uses a single embedding module per variable
536 type and aggregates visit-level embeddings within each type. Second, we do not consider additional longitudinal modules in the
537 decoder, as informed by the findings observed by Suh *et al.*²³ that such design does not bring benefits to overall data quality. Li
538 *et al.*⁴² also show that strong decoders can undermine longitudinal information in latent representations, thereby leading to VAE
539 posterior collapse and degraded generative performance in diffusion models. Third, we utilize a diffusion training paradigm
540 that is optimized for faster convergence rate and better data quality (i.e., FasterDiT) compared to the standard version²⁰.

541 We follow the two-stage training strategy of latent diffusion models³⁴, where we train the VAE in the first stage, and the
542 diffusion model in the second. To generate synthetic longitudinal records with the trained MeLD, we first sample a visit
543 sequence in the latent space from the learned diffusion model and then decode it through the VAE decoder to obtain the synthetic
544 record in the original data space. More concretely, the model input $\mathbf{X} = \{\mathcal{X}, \mathcal{T}, \mathcal{E}, \mathcal{P}, \mathcal{M}\}$, comprising real data matrix,
545 timestamps, EOS tokens, padding masks, and missingness indicators, is fed into the VAE encoder $\text{Enc}(\cdot)$ to derive the mean μ_z
546 and variance σ_z^2 of the latent posterior distribution $p(\mathbf{Z}|\mathbf{X})$. For the reconstruction task, variational samples drawn from this
547 posterior, $\mathbf{z} \sim p(\mathbf{Z}|\mathbf{X})$, are provided to the decoder $\text{Dec}(\cdot)$ and diffusion for their training. This architecture forces the encoder
548 to learn semantically rich latent representations that capture temporal dynamics, variable dependencies, sequence lengths, and
549 missingness patterns. As a result, latent samples generated by the diffusion model inherently encode the information necessary
550 to generate mixed-type, variable-length longitudinal cohort data.

551 During data generation, novel latent samples \mathbf{z}' are first produced by the diffusion model and then provided to the VAE
552 decoder, which generates synthetic data matrix \mathcal{X}' , EOS tokens \mathcal{E}' , and missingness indicators \mathcal{M}' . The synthetic data
553 are subsequently reconstructed into a meaningful visit-level representation by applying \mathcal{E}' and \mathcal{M}' to \mathcal{X}' . This process
554 yields tabular data in which each row represents a clinical visit of an individual, accommodating variable-length follow-ups,
555 mixed-type variables, and missing values. For evaluation, we post-process the MeLD-generated data by imputing missing
556 values with MICE, following the same preprocessing procedure applied to the real data. In addition, we retain an unimputed
557 version to evaluate the missingness patterns in the synthetic data.

558 The first stage trains a VAE with a 256-dimensional hidden layer, two-layer GRU and MLP modules, and an eight-head
 559 transformer with 64 channels. It is optimized with a batch size of 128 to yield latent representations with 32-dimensional latent
 560 size. The second stage trains a transformer-based diffusion with a 256-dimensional hidden size and eight layers of eight-head
 561 attention, using a batch size of 1,024.

562 **VAE loss**

563 The objective function of VAE minimizes the combined loss of the data reconstruction term, \mathcal{L}_{RE} , and the KL-divergence term,
 564 \mathcal{L}_{KL} , which measures the divergence between the posterior distribution $p(\mathbf{Z}|\mathbf{X})$ and the prior $p(\mathbf{Z})$:

$$565 \quad \mathcal{L}_{VAE} = \mathcal{L}_{RE} + \mathcal{L}_{KL}. \quad (1)$$

566 **Reconstruction Loss:** Due to the mixed-type, variable-length nature of clinical cohort data, different loss functions are
 567 needed: we use mean square error (MSE) normalized by time for continuous variables, and cross-entropy loss normalized by
 568 time for categorical variables and special tokens.

569 First, taking special tokens into account, we calculate the reconstruction loss for **continuous variables** as:

$$570 \quad \mathcal{L}_{continuous} = \frac{\sum_{t=1}^T \mathbf{1} \cdot \left(\sum_{i=1}^N \left(\mathbf{x}_{i,t}^C - \mathbf{y}_{i,t}^C \odot (\mathbf{1} - \mathbf{y}_{i,t}^{pad}) \right)^2 \odot (\mathbf{1} - \mathbf{x}_{i,t}^M) \odot (\mathbf{1} - \mathbf{x}_{i,t}^M) \right)}{\sum_{i=1}^N \sum_{t=1}^{t_i} \sum_{j=1}^s (1 - x_{i,t,j}^M)}, \quad (2)$$

571 where \mathbf{y} represents the reconstructed data and \odot denotes the element-wise multiplication operation. This design excludes
 572 imputed values from the loss calculation to maintain the model's robustness to imputation quality.

573 Second, we calculate the reconstruction loss for **categorical variables** as:

$$574 \quad \mathcal{L}_{categorical} = \frac{\sum_{t=1}^T \mathbf{1} \cdot \left(\sum_{j=1}^k \text{CrossEntropy} \left(\mathbf{x}_{:,t,j}^D, \mathbf{y}_{:,t,j}^D \odot (\mathbf{1} - \mathbf{y}_{:,t}^{pad}) \right) \odot (\mathbf{1} - \mathbf{x}_{:,t}^{pad}) \right)}{k \sum_{i=1}^N t_i}, \quad (3)$$

575 where we denote a visit vector containing all individuals as $\mathbf{x}_{:,t}$.

576 Next, we calculate the reconstruction loss for **missingness indicators** (treated as categorical variables) as:

$$577 \quad \mathcal{L}_{missing} = \frac{\sum_{t=1}^T \mathbf{1} \cdot \left(\sum_{j=1}^s \text{CrossEntropy} \left(\mathbf{x}_{:,t,j}^M, \mathbf{y}_{:,t,j}^M \odot (\mathbf{1} - \mathbf{y}_{:,t}^{pad}) \right) \odot (\mathbf{1} - \mathbf{x}_{:,t}^{pad}) \right)}{s \sum_{i=1}^N t_i}. \quad (4)$$

578 Finally, we calculate reconstruction loss for the **special EOS token** as:

$$579 \quad \mathcal{L}_{special} = \sum_{t=1}^T \mathbf{1} \cdot \text{CrossEntropy}(\mathbf{x}_{:,t}^{eos}, \mathbf{y}_{:,t}^{eos}) / T. \quad (5)$$

580 This loss is essential for enabling the model to learn the semantics of EOS and padding tokens and to generate records with
 581 variable lengths.

582 The total reconstruction loss is the sum of the aforementioned four losses:

$$583 \quad \mathcal{L}_{RE} = \mathcal{L}_{continuous} + \mathcal{L}_{categorical} + \mathcal{L}_{missing} + \mathcal{L}_{special}. \quad (6)$$

584 **KL-divergence Loss:** The KL-divergence loss is

$$585 \quad \mathcal{L}_{KL} = \beta \cdot D_{KL} \left(N \left(\mu_z, diag(\sigma_z^2) \right), N(\mathbf{0}, \mathbf{I}) \right), \quad (7)$$

586 which is to minimize the divergence between the posterior, defined by $N(\mu_z, diag(\sigma_z^2))$, and the Gaussian prior $N(\mathbf{0}, \mathbf{I})$. We
 587 apply a weighting factor β to achieve a balance of smooth concentrated posterior function while maintaining its expressiveness.
 588 Such a mechanism is crucial to prevent posterior collapse (a phenomenon in which the posterior distribution is forced to a
 589 standard Gaussian), thereby avoiding a trivial Gaussian diffusion model⁴²⁻⁴⁴.

590 Diffusion loss

591 The VAE encoder reduces mixed-type variable-length clinical cohort data into a fixed-dimension continuous vector, which
592 enables us to employ a simpler design for the diffusion transformer similar to the ones used for image generation¹⁹. Given the
593 latent encodings \mathbf{z}_0 and Gaussian noise $\varepsilon \sim N(\mathbf{0}, I)$, the forward diffusion process defines a sequence of progressively noisier
594 samples as

$$\mathbf{z}_\tau = \alpha_\tau \mathbf{z}_0 + \sigma_\tau \varepsilon, \quad (8)$$

596 where α_τ and σ_τ are functions of the diffusion timestep $\tau \in (0, \infty)$. σ_τ increases with τ , whereas α_τ decreases. As a result, the
597 data distribution gradually approaches an isotropic Gaussian as $\tau \rightarrow \infty$. The corresponding reverse process learns to iteratively
598 denoise samples by estimating the noise $\varepsilon_\theta(\mathbf{z}_\tau, \tau)$ at each timestep. A diffusion model can be trained with a simple MSE loss
599 between added noise and the predicted noise, which allows the accurate reconstruction of the target distribution $p(\mathbf{z}_0)$ during
600 sampling²⁴:

$$\mathcal{L}_{\text{Simple}}(\theta) = \|\varepsilon - \varepsilon_\theta(\mathbf{z}_\tau, \tau)\|_2^2. \quad (9)$$

602 Alternatively, the reverse process can be formulated as a probability flow ordinary differential equation (ODE) that
603 transforms a Gaussian noise to the target distribution $p(\mathbf{z}_0)$ ^{45,46}. In this formulation, the ODE is governed by a conditional
604 velocity field $\mathbf{v}(\mathbf{z}, \dot{\tau}) = \dot{\alpha}_\tau \mathbb{E}[\mathbf{z}_0 | \mathbf{z}_\tau = \mathbf{z}] + \dot{\sigma}_\tau \mathbb{E}[\varepsilon | \mathbf{z}_\tau = \mathbf{z}]$, where $\dot{\alpha}$ and $\dot{\sigma}$ are functions of $\dot{\tau} \in [0, \dot{T}]$. It represents the expected
605 direction and rate at which a noisy sample \mathbf{z} should change at time $\dot{\tau}$ in order to move toward the target distribution $p(\mathbf{z}_0)$. This
606 quantity can be estimated using a neural network $\hat{\mathbf{v}}_\theta(\mathbf{z}_\tau, \dot{\tau})$. Thus, a diffusion model can also be trained with the flow matching
607 objective:

$$\mathcal{L}_{\text{Flow}}(\theta) = \int_0^{\dot{T}} \mathbb{E} [\|\mathbf{v}_\tau - \hat{\mathbf{v}}_\theta\|^2] d\tau = \int_0^{\dot{T}} \mathbb{E} [\|\hat{\mathbf{v}}_\theta(\mathbf{z}_\tau, \dot{\tau}) - \dot{\alpha}_\tau \mathbf{z}_0 - \dot{\sigma}_\tau \varepsilon\|^2] d\tau. \quad (10)$$

609 Empirical evidence²⁰ has shown that Eq. 10 achieves superior performance and higher sampling efficiency than Eq. 9. Yao
610 et al.²⁰ propose a linear schedule ($\dot{T} = 1$, $\dot{\alpha}_t = t$ and $\dot{\sigma}_t = 1 - t$) for the ODE strategy and develop FasterDiT. In addition,
611 FasterDiT uses cosine regularization to encourage similar samples to cluster in hidden space, a strategy conceptually aligned
612 with the regularization proposed by Wang et al.⁴⁷. Taken together, the objective function used for tuning MeLD's diffusion
613 model is:

$$\mathcal{L}_{\text{FasterDiT}}(\theta) = \int_0^1 \mathbb{E} \left[\|\mathbf{v}_\tau - \hat{\mathbf{v}}_\theta\|^2 + \left(1 - \frac{\mathbf{v}_\tau \cdot \hat{\mathbf{v}}_\theta}{\|\mathbf{v}_\tau\| \|\hat{\mathbf{v}}_\theta\|}\right) \right] d\tau. \quad (11)$$

615 Evaluation framework

616 To account for randomness in model training, we train each model independently twice. Each trained model then generates five
617 synthetic datasets. Thus, a total of ten datasets are used for evaluating the underlying model's capability. These ten datasets,
618 referred to hereafter as replicates, are generated using distinct random seeds and maintain the same sample size as the real
619 training data. For all evaluation metrics, we report the mean and 95% CIs across replicates. The 95% CIs are constructed
620 with normal approximation, with the mean and standard deviations of ten replicates serving as the estimates of the sampling
621 distribution's parameters. To ensure fair comparison among models that cannot directly handle missing data, missing values in
622 real data are imputed prior to evaluation. We now describe the evaluation metrics used to assess data utility, fidelity, and privacy.

623 Time-to-event estimation

624 All medical events and their corresponding timestamps are extracted for each individual. For a given event, e.g., a diagnosis
625 of a certain disease (clinical endpoint), if it does not occur in an individual's medical history, then this individual is treated
626 as censored for this clinical endpoint, with the time of the last recorded visit used as the censoring time. We calculate both
627 Kaplan-Meier and Nelson-Aalen estimates: the Kaplan-Meier estimator is used for quantifying differences between survival
628 curves, whereas the Nelson-Aalen estimator is chosen for visualization. Two Kaplan-Meier-based methods are used to evaluate
629 differences between survival curves. The log-rank test compares the observed and expected numbers of events between
630 groups at each event time, and aggregates these differences across all event times to assess whether survival curves differ,
631 assuming equal survival under the null hypothesis. The log-rank test is widely used to compare survival distributions between
632 groups. However, it has limited power when survival curves cross or when differences occur late in follow-up, as the number
633 of individuals at risk diminishes. To complement the log-rank test, we compute the non-parametric Kaplan-Meier distance
634 (KM-D)²⁶, calculated as the mean absolute difference between two Kaplan-Meier curve estimates evaluated at 1,000 equally
635 spaced time points from time 0 to the last observed event in the shorter curve.

636 In addition, we evaluate the maximum follow-up time T_{max} in a cohort as a supplement metric to show if synthetically
637 generated data fail to reproduce the maximum observation time in real data.

638 Time-to-diagnosis analysis focuses on the time from ART initiation to the first recorded diagnosis of a clinical endpoint.
639 We perform the log-rank tests across all 50 clinical endpoints and apply a Bonferroni correction to adjust for multiple tests,

640 which yields an adjusted significance threshold of 0.0001. We then report the overall false discovery rate (FDR), as well as the
641 mean of KM-D calculated from 50 clinical endpoints over ten replicates.

642 **Prediction**

643 An important use case of synthetic clinical cohort data is to support the development of outcome prediction models. We
644 select three representative disease prediction tasks and use data observed during the first 180 days since program enrollment
645 as predictors to predict whether an individual will subsequently develop the disease. Individuals are excluded if they were
646 diagnosed within the first 180 days or their total follow-up time is shorter than 180 days. In data preprocessing, PWH from
647 Haiti are excluded from analysis as relevant clinical endpoints are unavailable. All available variables, including demographics,
648 weight, height, CD4 cell count, HIV viral load, ART regimens, and clinical diagnoses, are utilized as predictors. A two-layer
649 GRU model with 256 hidden units is trained, with a 9:1 random training-validation split. Early stopping with a patience of five
650 epochs is utilized to determine the end point of model training. Model performance is evaluated using AUROC on real test
651 dataset, comparing the reference model trained on real training data against models trained on synthetic datasets.

652 **Risk factor estimation**

653 Risk factor estimation assesses how well synthetic data reproduce the clinically meaningful associations observed in real data.
654 We first construct the survival dataset based on the longitudinal cohort data of PWH by defining the time-to-event and censoring
655 indicators and identifying the baseline risk factors, including sex, age, CD4 cell count, and calendar year at ART initiation.
656 Then the Cox-proportional hazard model is used to estimate hazard ratios, following model specifications consistent with
657 published epidemiology research using CCASAnet data^{28,48}. Estimates obtained from models fitted on real training data serve
658 as the reference for comparison.

659 While there is no consensus on how to evaluate data utility in risk factor estimation, we propose a set of complementary
660 metrics for this purpose. First, with the statistical significance set at 0.05 and the estimates from real data as the “ground-truth”,
661 we count type I and type II errors in inferences derived from synthetic data. We also calculate the number of direction errors,
662 which happen when the signs of statistically significant effects identified from the synthetic data are in the opposite direction to
663 those found in real data. Together, these errors measure how consistently analyses performed on synthetic data would lead to
664 the same conclusions in risk factor effects as those based on real data. Second, we compare the pooled effect estimates for
665 each risk factor using Rubin’s rule by combining the means and standard error estimates across ten synthetic replicates. This
666 evaluation is used to assess the magnitude of discrepancies between estimated effects based on real and synthetic data.

667 To dive deeper into the numerical differences in the estimates, we also report the following metrics in Supplementary
668 Table 5: 1) bias, averaged over the ten replicates, which quantifies the deviation between estimates from the synthetic data and
669 those from real data, i.e., $\beta_{syn} - \beta_{real}$, 2) standard error (SE) ratio, calculated as the ratio of the SE derived from synthetic data
670 to that from real data, averaged over the ten replicates, i.e., se_{syn}/se_{real} , and 3) CI coverage, calculated as the fraction of the real
671 CI that is covered by the CI derived from synthetic data, normalized by the total span of their union to account for potentially
672 wider synthetic CIs. This metric assesses both the estimate deviations and their uncertainty.

673 **Variable-level distributions**

674 To quantify variable-level fidelity, we calculate the distances between real and synthetic distributions for both continuous
675 and categorical variables. For each continuous variable, we calculate the Wasserstein distance (WSD) between its marginal
676 distribution in real training data and in each synthetic data replicate. WSD measures the minimum amount of probability mass
677 that must be transported to transform one distribution into another. We report the mean WSD across all replicates along with
678 the corresponding 95% CI.

679 For categorical variables, we evaluate the frequencies of individual variables (i.e., medical concepts encompassing diagnoses
680 and treatment regimens), their bigrams (i.e., co-occurrences within the same visits), and sequential bigrams, representing
681 pairs of concepts observed in two consecutive visits. The evaluations are conducted at both the person and visit levels. In the
682 person-level analysis, multiple occurrences of the same medical concept or concept pair across an individual’s visits are counted
683 only once, whereas in the visit-level analysis, each occurrence of a concept or concept pair is counted separately. Specifically,
684 concept probability focuses on the occurrence of individual medical concepts, while bigram probability captures how often two
685 distinct medical concepts co-occur within the same visit. In contrast, sequential bigram probability measures the frequency
686 with which a concept pair appears across consecutive visits.

687 For both person- and visit-level analyses, we then derive the aggregate differences between the real training and synthetic
688 datasets using mean absolute error (MAE), which characterizes the magnitude of the differences. We report the means and
689 corresponding 95% CI across ten replicates.

690 **Correlation**

691 While correlation is a standard metric for evaluating synthetic cross-sectional data fidelity, it has rarely been applied in the
692 longitudinal data setting. To address this issue, we propose to evaluate two types of correlations: between-individual and

693 within-individual correlations. For the between-individual correlation, we first compute the mean of each variable across all
694 visits for each individual $\bar{\mathbf{x}}_i$, and then derive variable-variable correlations using Spearman's rank correlation coefficients,
695 chosen because of the mixed data types. For the within-individual correlation, we first center each individual's variable values
696 using the corresponding variable-level mean across all visits $\mathbf{x}'_i = \mathbf{x}_i - \bar{\mathbf{x}}_i$ and then calculate variable-variable correlations on the
697 centered data matrix \mathbf{X}' using the same Spearman correlation method. For both correlation types, the absolute differences of the
698 correlation matrices calculated from the real training and synthetic datasets are aggregated using Frobenius norm to provide
699 an overall measure of the discrepancy. We report the mean of Frobenius norm distances across ten replicates, as well as the
700 corresponding 95% CI.

701 **Latent clustering consistency**

702 We employ latent clustering analysis to assess how effectively a synthetic data generation model captures the joint distribution
703 of real data in the latent space. At a high level, we perform data clustering over the combined set of real and synthetic data and
704 then investigate the composition of each resulting cluster to assess how well the two data sources are intermixed.

705 We reshape the 3D data matrix of size $(N, T, s+k)$ into a 2D matrix of size $(N, T \times (s+k))$, where each row represents the
706 complete record of an individual. For computational efficiency, 5,000 records are randomly selected from both the real training
707 and synthetic datasets, resulting in a combined total of 10,000 records. We then perform principal component analysis (PCA) to
708 the merged datasets, and select the principal components that explain 80% of total variance to project the data from the original
709 space into a latent space. K -means clustering is then applied across a range of clusters number K from 2 to 10, and the optimal
710 K is selected as the one that leads to the smallest silhouette distance. With all clusters identified, normalized mutual information
711 (NMI) is calculated to measure the agreement between two clustering assignments: the cluster labels produced by K -means
712 versus the true labels (real versus synthetic):

$$713 \quad \text{NMI}(\mathbf{U}, \mathbf{V}) = \frac{2I(\mathbf{U}; \mathbf{V})}{H(\mathbf{U}) + H(\mathbf{V})}, \quad (12)$$

714 where $I(\mathbf{U}; \mathbf{V})$ is the mutual information between partitions \mathbf{U} and \mathbf{V} , and $H(\cdot)$ denotes entropy. We report the mean NMI and
715 the corresponding 95% CI calculated from ten replicates.

716 **Medical concept abundance**

717 The above data fidelity metrics all evaluate variables and their interrelationships. To examine whether information at the
718 individual level is also well preserved, we measure the medical concept abundance (MCA)⁴, a metric originally designed
719 for assessing synthetic cross-sectional health data. MCA serves as a proxy of a population's distribution of illness burden or
720 health status, which enables evaluating how faithfully synthetic data reflect real individual-level health distributions. In the
721 cross-sectional context, MCA for an individual is computed by counting the number of distinct medical concepts documented
722 in their record:

$$723 \quad MCA_i = \sum_{j=1}^K \mathbf{1}(Concept_{i,j}), \quad (13)$$

724 where K denotes the size of the medical concept space. To quantify the difference in MCA between real and synthetic data, the
725 empirical MCA distributions built from the real and synthetic datasets are first discretized to a fixed number of bins and then
726 normalized. The Manhattan distance of the two discretized distributions is reported.

727 To extend the original MCA metric to longitudinal clinical records with variable visit sequence lengths, we calculate the
728 total occurrences of medical concepts within individual i 's longitudinal record and then normalize it by the number of visits t_i :

$$729 \quad MCA_i = \sum_{t=1}^{t_i} \sum_{j=1}^K \mathbf{1}(Concept_{i,t,j}) / t_i. \quad (14)$$

730 In this study, we consider all clinical diagnoses and treatment events as medical concepts. The same distance measure described
731 above is then applied to quantify the longitudinal MCA difference between the real and synthetic datasets. We report the mean
732 distance of MCA and the corresponding 95% CI calculated from ten replicates.

733 **Missingness pattern**

734 The definition of data missingness varies across disciplines and applications. In this study, for evaluation purposes, we treat
735 all unobserved measurement values in each visit (i.e., CD4 cell count, HIV viral load, weight, and height) as missing data,
736 whether they are unmeasured, intentionally omitted, or below the detection limits. With $x_{i,t,j}^M \in \{0, 1\}$ defined as the missingness
737 indicator for individual i , visit t and variable j , two measures are considered: 1) variable-level proportion of missingness,
738 defined as the overall missingness proportion for variable j , $\frac{\sum_{i=1}^N \sum_{t=1}^{t_i} x_{i,t,j}^M}{\sum_{i=1}^N t_i}$, and 2) individual-level proportion of missingness,

739 defined as the missingness proportion for variable j within an individual, $\frac{\sum_{t=1}^{t_i} x_{i,t,j}^M}{t_i}$. We report the mean and 95% CI of both
740 proportions in synthetic data replicates and the real training dataset.

741 **Privacy**

742 Privacy evaluation focuses on three types of risks: attribution inference, membership inference, and nearest neighbor adversarial
743 accuracy (NNAA). Following the approach of Theodorou *et al.*²², all continuous variables are discretized into 30 quantile-based
744 bins, which converts the entire dataset into a representation of binary medical concepts to facilitate consistent risk assessment.
745 And for each experiment, we report the mean and corresponding 95% CI calculated from ten replicates.

746 For attribute inference attacks, an adversary is assumed to possess partial knowledge of real individual's records, and leverage
747 the released synthetic data to infer the sensitive attributes that remain unknown. Here, we assume the adversary has the prior
748 knowledge of demographic information and the 100 most frequently occurring concepts for inferring the remaining sensitive
749 information. We randomly sample 5,000 records from the real training dataset and another 5,000 from the synthetic dataset.
750 Using Hamming distance, each real record's unknown attributes are predicted based on its K -nearest neighbors in the synthetic
751 data through majority voting. In this experiment, we set $K = 1$ as in Theodorou *et al.*²², and report the mean F1 score of the
752 inferred attributes as the measure of attack success.

753 A membership inference attack happens when an adversary attempts to infer whether a complete real record they possess
754 is included in the dataset used to train the synthetic data generation model. In this experiment, we simulate such an attack
755 dataset by randomly sampling 5,000 records each from the real training and real test data. For each record in this attack set, we
756 calculate its Hamming distance to its nearest neighbor record in the synthetic dataset. The median of these nearest neighbor
757 distances is used as the cutoff threshold for inference, i.e., any real record with its nearest neighbor distance to the synthetic
758 dataset below the cutoff threshold is predicted to be a member of the real training data. We also experiment with a wide range
759 of distance cutoffs and construct ROC curves in Supplementary Fig. 4.

760 Nearest-neighbor adversarial accuracy (NNAA) evaluates potential overfitting in the synthetic data generation model by
761 examining the degree to which the generated synthetic data are systematically closer to the real training data than to the real test
762 data. In this experiment, 5,000 records are randomly sampled each from real training (T), real test (E) and synthetic dataset (S).
763 For each dataset, we calculate the Hamming distance of each record to its nearest neighbor within the same dataset, and the
764 distance to the nearest neighbor in another dataset. We then compare the two distances and calculate the proportion of records
765 that are closer to the same dataset compared to other. For instance, we denote the shortest distance of record i in the synthetic
766 dataset to the remaining records as $d_{SS}(i)$, and the shortest distance to those in the training dataset as $d_{ST}(i)$, and then calculate
767 the proportion of records in the synthetic dataset that are closer to the same dataset than to the training dataset as:

$$768 \quad p_{ST} = \frac{1}{n} \sum_{i=1}^n 1(d_{ST}(i) > d_{SS}(i)). \quad (15)$$

769 Similarly, we calculate these proportions for p_{TS} , p_{SE} , and p_{ES} . If a model does not overfit to its training data, these quantities
770 are expected to be close to 0.5. Otherwise, p_{ST} and p_{TS} would be less than 0.5. Overall, we summarize the risk of overfitting as:

$$771 \quad NNAA = 0.5 \times (p_{SE} + p_{ES}) - 0.5 \times (p_{ST} + p_{TS}), \quad (16)$$

772 where a positive NNAA value that exceeds a widely accepted threshold (e.g., 0.03 by Yale *et al.*³¹) can raise privacy concerns.

773 **Ranking**

774 To summarize each model's overall strengths and weaknesses across evaluation metrics, we first rank all synthetic datasets
775 generated by the five models (ten replicates per model, totaling 50 synthetic datasets) according to their evaluation results in
776 each metric type. From these data rankings, we then derive normalized model rankings. Lower ranks correspond to higher
777 performance. All model ranks are then linearly normalized to a range from 1 (best) to 5 (worst). Specifically, for each evaluation
778 metric, we rank the 50 synthetic datasets based on their metric values and then compute each model's rank by averaging
779 the normalized ranks of their ten replicates. For metrics falling within the same type, for example, the outcome prediction
780 performance across three outcomes, we further update each model's rank as the average across these metrics. Finally, we
781 present model rankings within the utility, fidelity, and privacy dimensions and visualize them using radar plots (Fig. 1e).

782 Data Availability

783 Both the original and synthetic CCASAnet datasets are available upon request. In accordance with the CCASAnet Principles
784 of Collaboration, applicants seeking synthetic data need to submit a concept sheet outlining the intended use of the data. All
785 requests will be reviewed by the CCASAnet Executive Committee. To access the original de-identified CCASAnet data,
786 applicants must complete a more extensive concept sheet and a data use agreement with Vanderbilt University Medical Center.
787 Applications for access to both datasets should be submitted at <https://redcap.link/ccasanetsharingrequest>. The CCASAnet
788 Executive Committee will start processing applications upon the publication of this study.

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797 Author Contribution Statement

798 Z.J.L., C.Y., B.E.S., and B.A.M. conceived the study and designed the experiments. Z.J.L. conducted data preprocessing,
799 performed the experiments, and analyzed the results. Z.L. and N.J. contributed significantly to the model and study design.
800 Z.J.L. and C.Y. summarized the major experimental findings and drafted the manuscript. B.E.S. and B.A.M. assisted in
801 interpreting the results and extensively revised the manuscript. Z.L., N.J., A.A., A.B., J.M.P., S.N.D., Y.C., R.I., F.P., J.B., D.V.,
802 and C.C. provided intellectual input and contributed to manuscript revisions. C.Y., B.E.S., and B.A.M. jointly supervised the
803 study and serve as corresponding authors. All authors participated in manuscript preparation and approved the final version.

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